Before starting...

If you are interested in taking part in some of **our research studies**, please scan the **QR code** and fill out the form.

A member of our research team will get in touch with you (there is no obligation to participate if our free slots are not compatible with your schedule).

https://forms.gle/FEVR9Uwa75mEEC1r5

Your next presentation:

On Thursday (6th November)

Main topics :

**How the doctor-patient relationship shapes the brain
or/and
How context modulates neural processes**

Key words: Contextual factors, Placebo and nocebo mechanisms, Neurobiology of trust, Neuroplasticity in clinical interaction

You will have time at the end of both of my lectures to start your presentations

Placebo, nocebo and contextual factors:

HOW DOES CONTEXT CHANGES OUR BRAIN?

History, research and clinical practice

THEORETICAL SUMMARY

- Definitions
- Psychological mechanisms that activate placebo and nocebo effects
- Physiological mechanisms that activate placebo and nocebo effects
- From theory to clinical practice and ethics

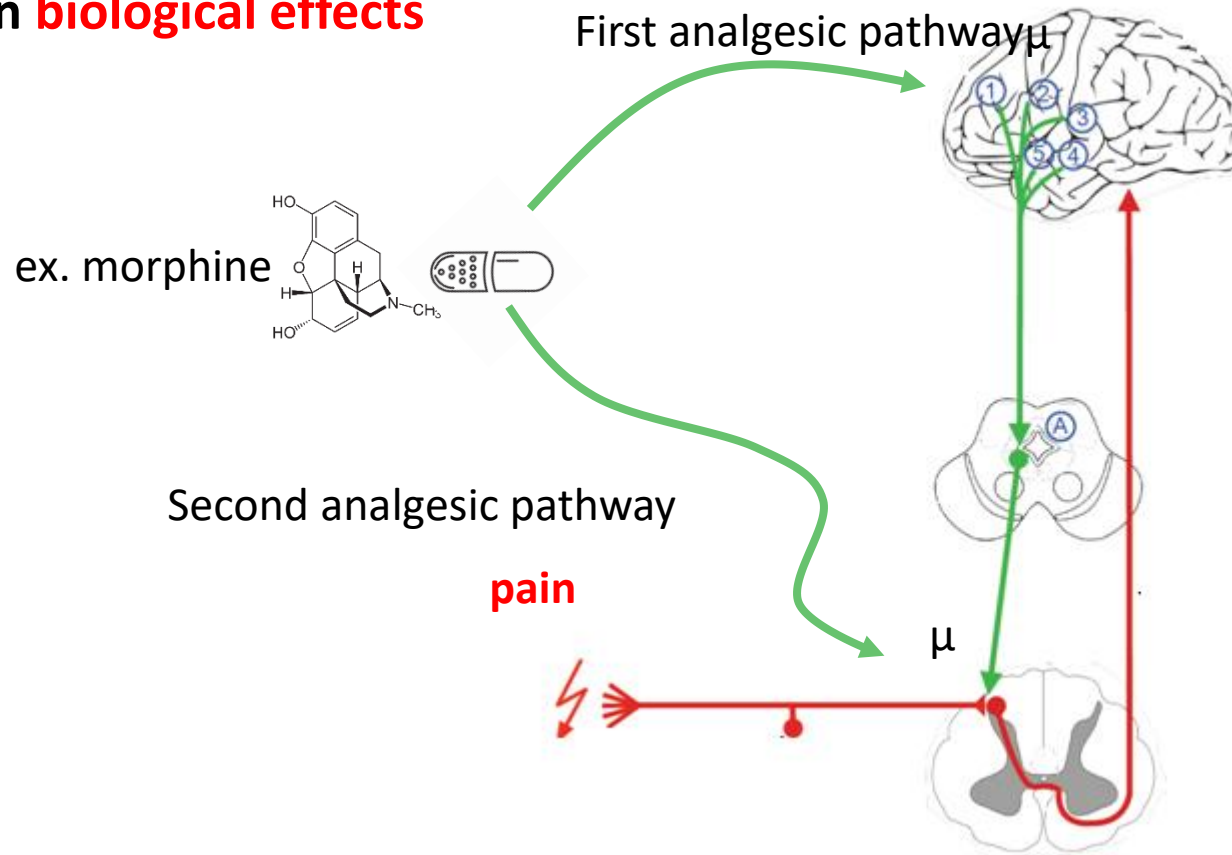# Pharmacological Treatment

masculine noun

A substance capable of causing functional changes in the body by means of a chemical or physical action
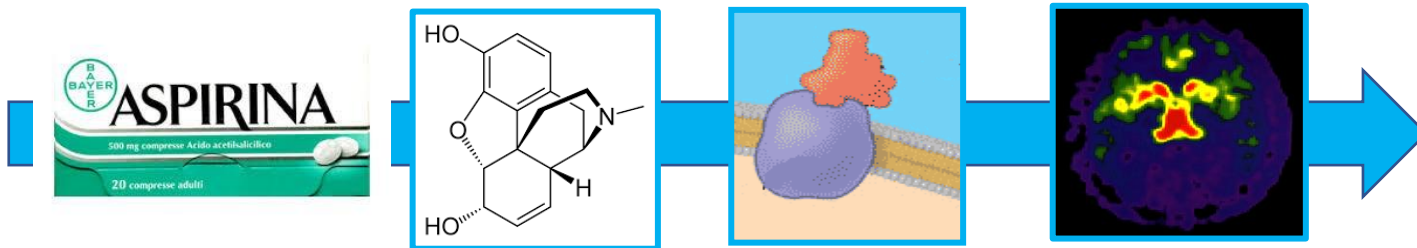
PHARMACOLOGICAL TREATMENT

- **molecule** introduced into the body
- has certain **biochemical actions**
- has certain **biological effects**

First analgesic pathway µ

ex. morphine

Second analgesic pathway

pain

µ

PHARMACOLOGICAL TREATMENT

- **Pharmacodynamics:** study of the biochemical and physiological effects of drugs on the body, and their mechanism of action

- **Pharmacokinetics:** study of the effects that the body's processes have on the drug (absorption, distribution, metabolism, elimination)

pharmacological treatment

From pharmacological treatments to other treatments

Surgical treatment

Pharmacological treatment

Manual therapies

Psychotherapy

HOW CAN WE SAY THAT A TREATMENT IS EFFECTIVE?
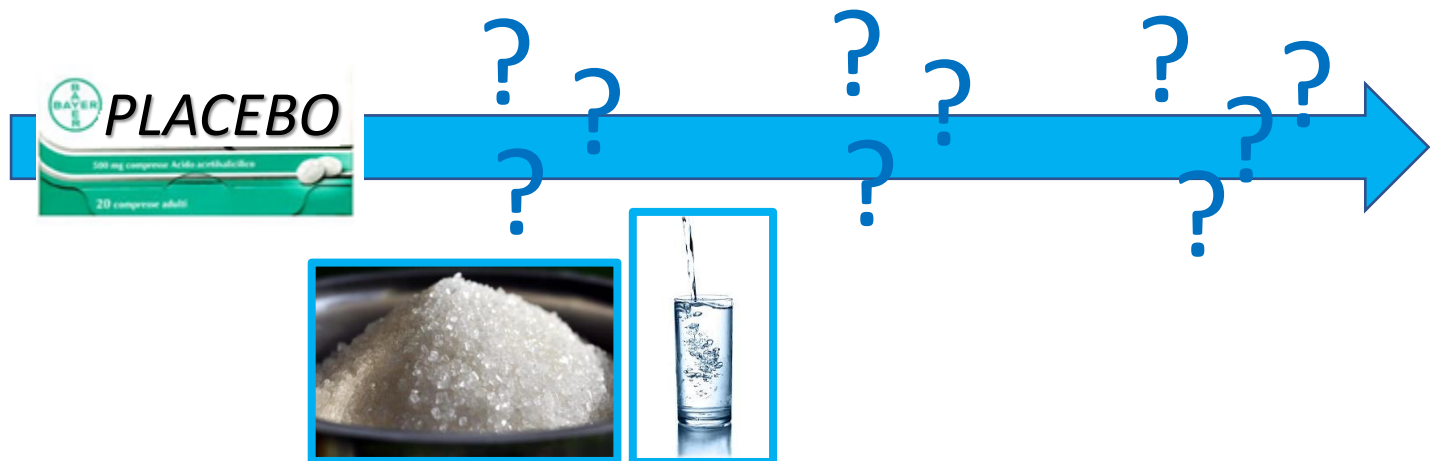
DEFINITIONS

placebo

/pla·cè·bo/

masculine noun

Inert substance, with no specific effects

PLACEBO in modern science: 3 contexts

- In **clinical trials** → the aim is to **REDUCE** the placebo effect

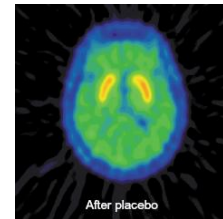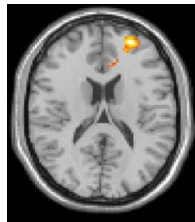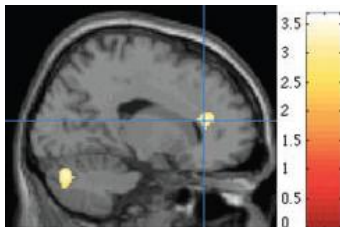ANALYSIS   EVIDENCE   CLINICAL STUDY   EFFECTIVENESS   MEDICATIONS   HEALTH

- In scientific research → the aim is to **UNDERSTAND** how placebo effect works

- In clinical practice → the aim is to **INCREASE** the placebo effect

PLACEBO in modern science: 3 contexts

- **In clinical trials→ the aim is to REDUCE the placebo effect**

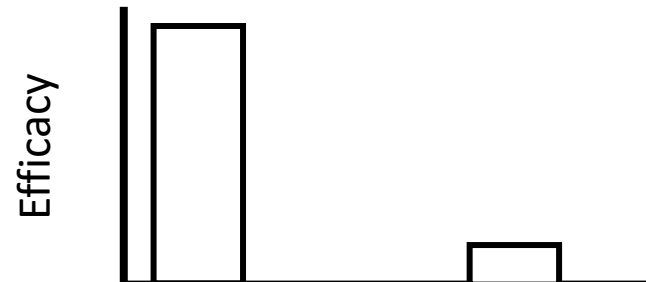ANALYSIS   EVIDENCE   CLINICAL STUDY   EFFECTIVENESS   MEDICATIONS   HEALTH

Placebo administered to quantify the efficacy of an active treatment

PLACEBO in modern science: 3 contexts

- **In clinical trials → REDUCE**

ANALYSIS   EVIDENCE   CLINICAL STUDY   EFFECTIVENESS   MEDICATIONS   HEALTH

ASPIRINA

PLACEBO

Efficacy

PLACEBO IN CLINICAL TRIALS

Placebo in modern science: distinguishing 3 contexts

- **In clinical trials**

→**Placebo as a control treatment to evaluate the efficacy of an active treatment**
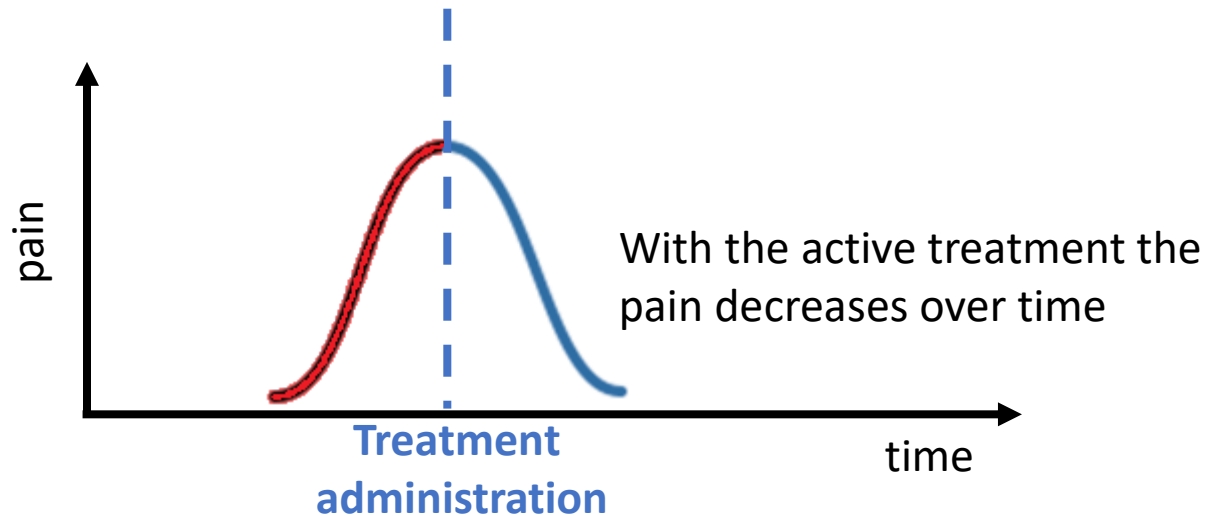
→**THE GOAL IS TO FIND TREATMENTS WITH SUPERIOR EFFICACY COMPARING TO PLACEBO**

PLACEBO IN CLINICAL TRIALS

PAIN CONDITION

We administer the ACTIVE treatment (active arm)

With the active treatment the pain decreases over time

pain

Treatment administration

time

PLACEBO IN CLINICAL TRIALS

PAIN CONDITION

We administer the ACTIVE treatment (active arm) and ...

WE COMPARE WITH PLACEBO (flat line)

In this case, is the drug more effective than placebo in reducing pain?

Pain remains the same over time

pain

Treatment administration

Time

PLACEBO IN CLINICAL TRIALS

PAIN CONDITION

We administer the ACTIVE treatment (active arm) and ...

WE COMPARE WITH PLACEBO (sine wave)

In this case, is the drug more effective than placebo in reducing pain?

pain

Treatment administration
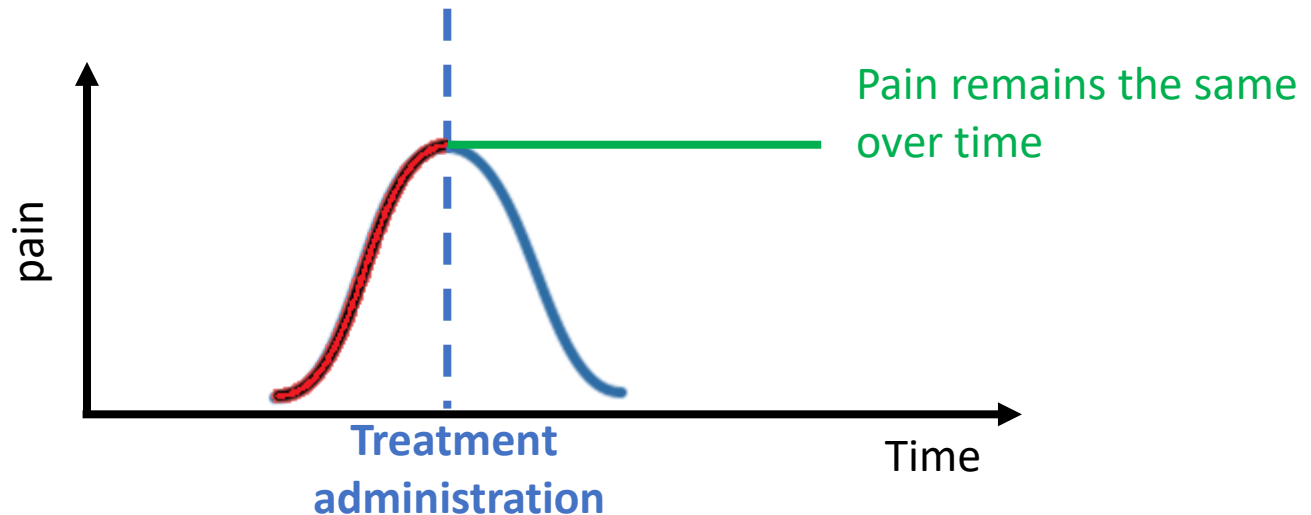
time

PLACEBO IN CLINICAL TRIALS

PAIN CONDITION

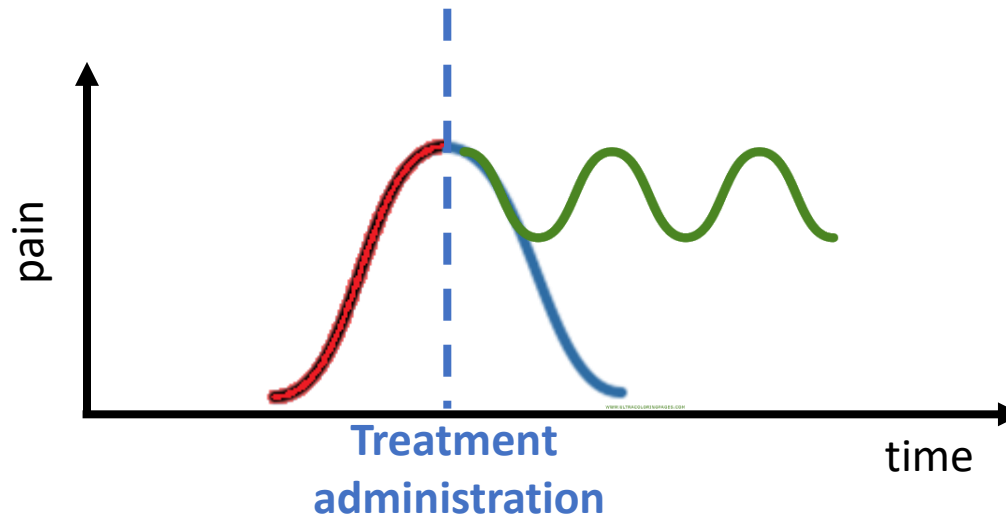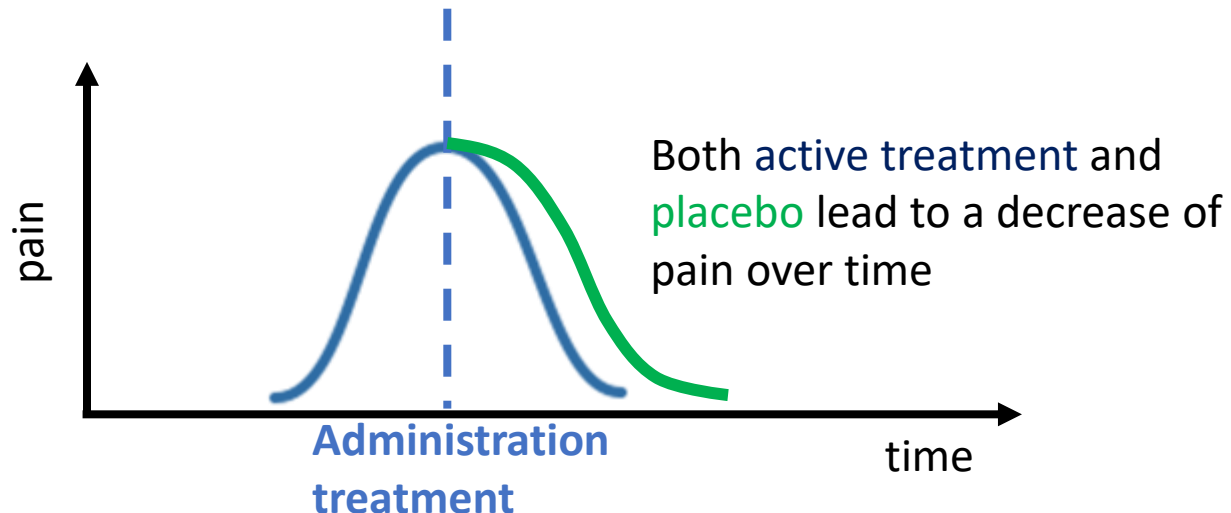**We administer the ACTIVE treatment (active arm) and ...**

WE COMPARE WITH PLACEBO

**In this case, is the drug more effective than placebo in reducing pain?**

pain

Administration treatment

time

Both active treatment and placebo lead to a decrease of pain over time

FACTORS THAT LEAD TO IMPROVEMENT

When we administer a treatment, this treatment can lead to an improvement due to several factors:

1) **Specific factors→ related to the treatment→ active principle**
2) **Methodological factors**
3) **Non-specific factors**

1 +/* 2 +/* 3

pain

Treatment administration

time

Treatment efficacy

METHODOLOGICAL FACTORS

NON-SPECIFIC FACTORS
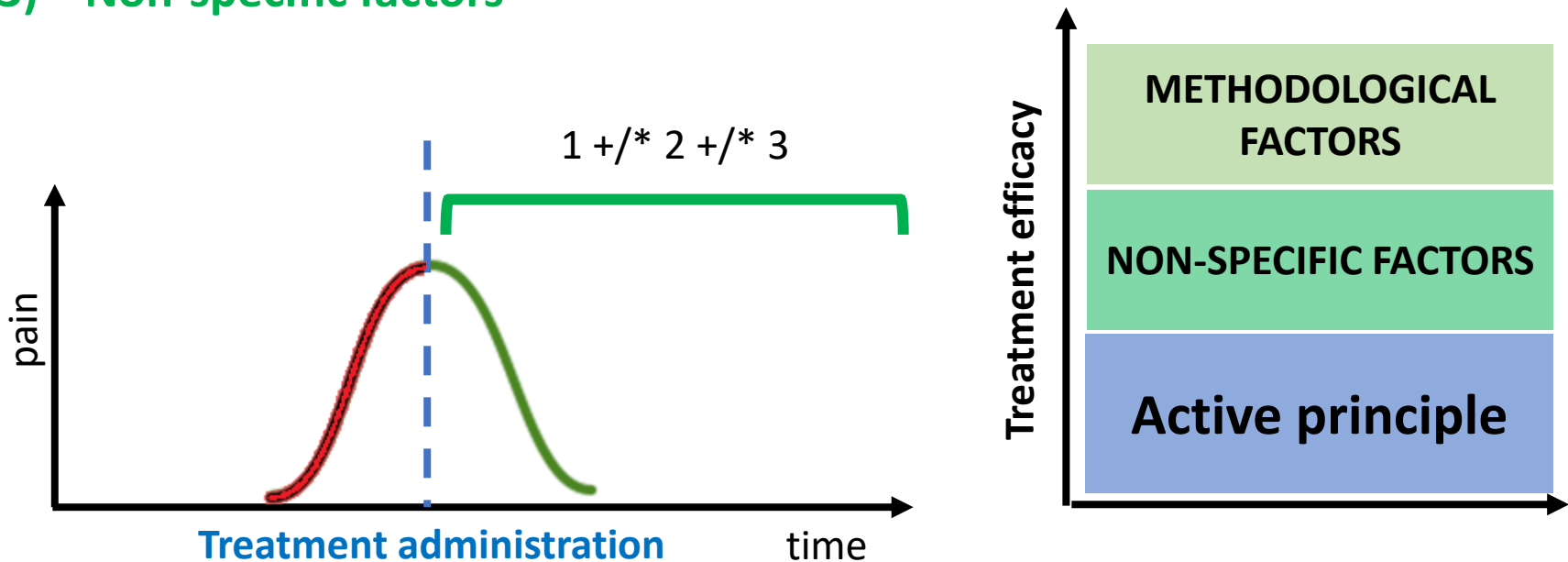
Active principle

The decrease of pain is the result of the methological factors, non specific factors and the active principle together

METHODOLOGICAL FACTORS: NATURAL REMISSION

- **Natural remission:** happens in a lot of conditions (e.g. Anxiety, Depression, Headache...) that have spontaneous fluctuations (**natural history of a disease**, a symptom).

- **Natural remission** → natural course of a symptom, of a disease, in the absence of specific interventions

- **ERROR**: Mistake the natural remission for the efficacy

- **SOLUTION:** introduce a control group in which the natural course of the disease/symptom is studied → "natural history group"

METHODOLOGICAL FACTORS: REGRESSION to the MEAN

- **Statistical phenomenon** (non-biological and non-psychological)

- If a variable is extreme at its first measurement, it will tend to be closer to the mean at its second measurement.

Example:

- A medication that lower blood sugar is tested on a patient with extremely high glucose levels.

- On a second measurement, the values are lower and closer to the population average

- This change may not be ddue to the modification, but rather to **regression to the mean** → the statistical tendency for extreme values to move closer to the average on repeated measures

METHODOLOGICAL FACTORS:
# BIASES , ambiguity of the symptom, errors

- **Hawthorne effect** (effect of being observed): people tend to work harder or perform better when they feel they are being watched or studied.

- **Pleasing the Experimenter:** participants may alter their behavior to fit what they believe the researcher expects or wants to see (consciously or unconsciously) in order to please the experimenter or confirm the study's hypotesis.

- **Measurement errors**

- **Use of subjective** (and non-objective) **scales to assess often ambiguous symptoms** (e.g. pain)

- **Unidentified co-interventions**

HOW CAN WE SAY THAT A DRUG (treatment) is EFFECTIVE?

- To control methodological factors→ we administer a **PLACEBO**

  ✓ **ACTIVE ARM: receives the active treatment**

  ✓**PLACEBO ARM: receives the placebo treatment**
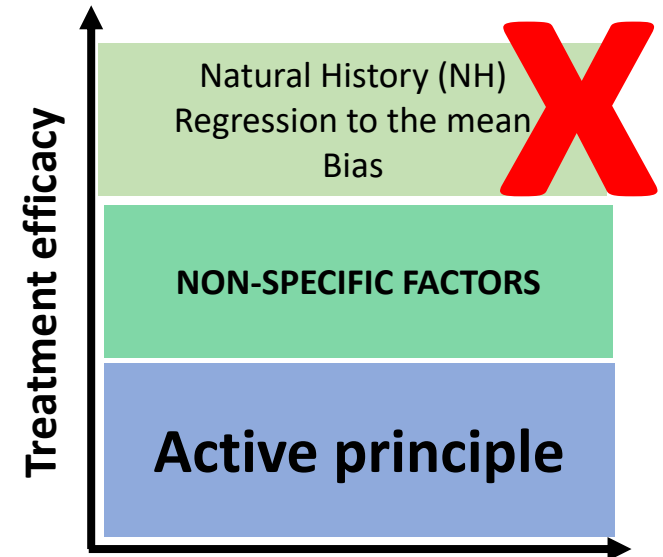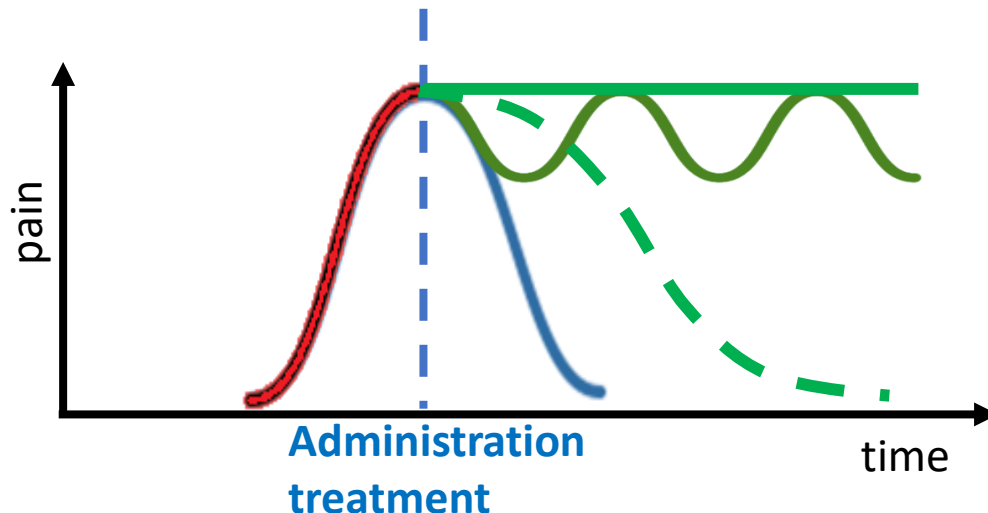
CLINICAL TRIALS

- **Gold standard** → RCT (**R**andomized – double blind – placebo controlled – **C**linical **T**rial)

- Examples of "historical" controlled trials:

1. Mesmerism (Mesmer, commissioned by Benjamin Franklin → there is no magnetic fluid, it is a matter of imagination or spontaneous remission)

2. Homeopathy (Hahnemann, bread tablets compared with homeopathic tablets → same effect!)

CLINICAL TRIALS

Research conducted to collect data on the safety and efficacy of new drugs, new clinical procedures or new medical devices.

They are conducted after the approval by competent authorities and an ethics committee.

They are characterized by PHASES (see phases of clinical trials).

Clinical trials in which participants receive a treatment whose effects are compared to **another treatment** or an **inert treatment** (placebo).
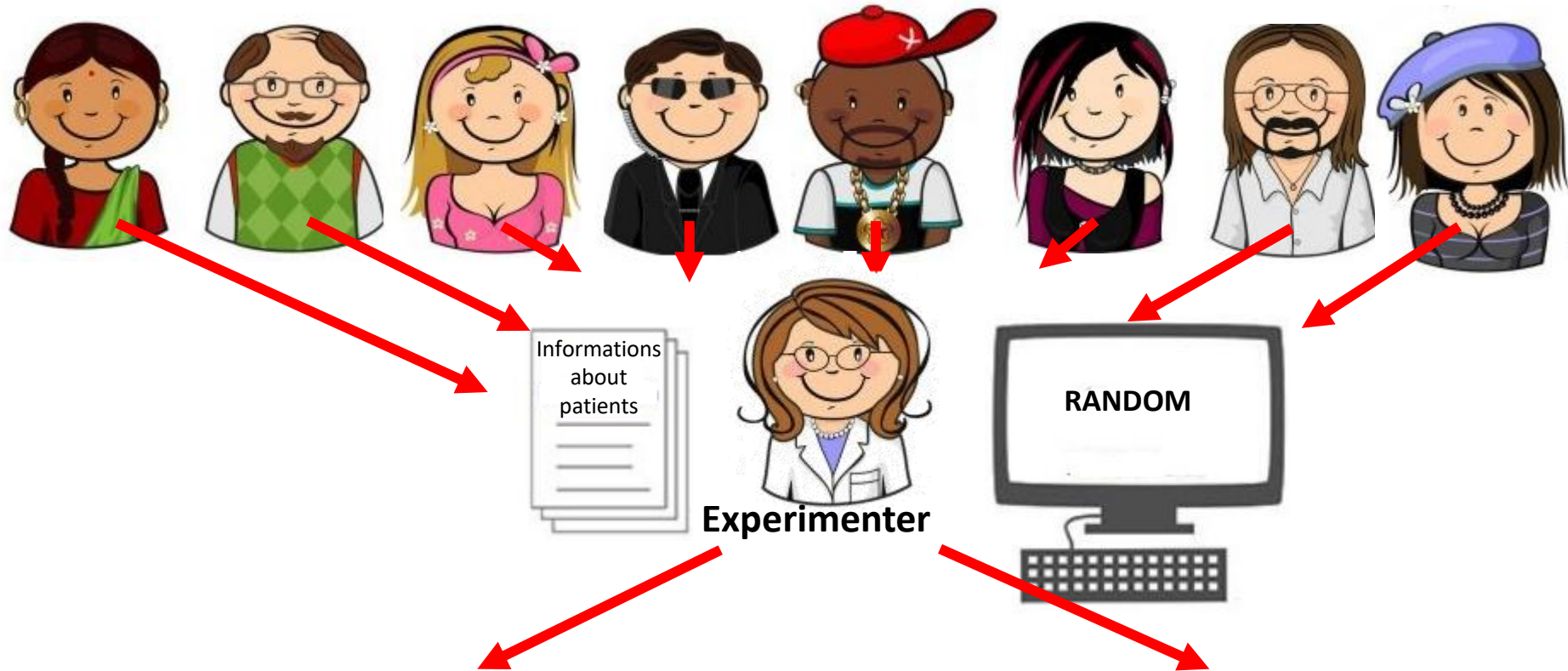
CLASSIFICATION OF CLINICAL TRIALS

- Method used to allocate participants to groups (treatment or control) **(randomized or non-randomized)**

- Participant and researcher awareness of group allocation **(blinding)**

CLASSIFICATION OF CLINICAL TRIALS: non-randomized method

Experimenter
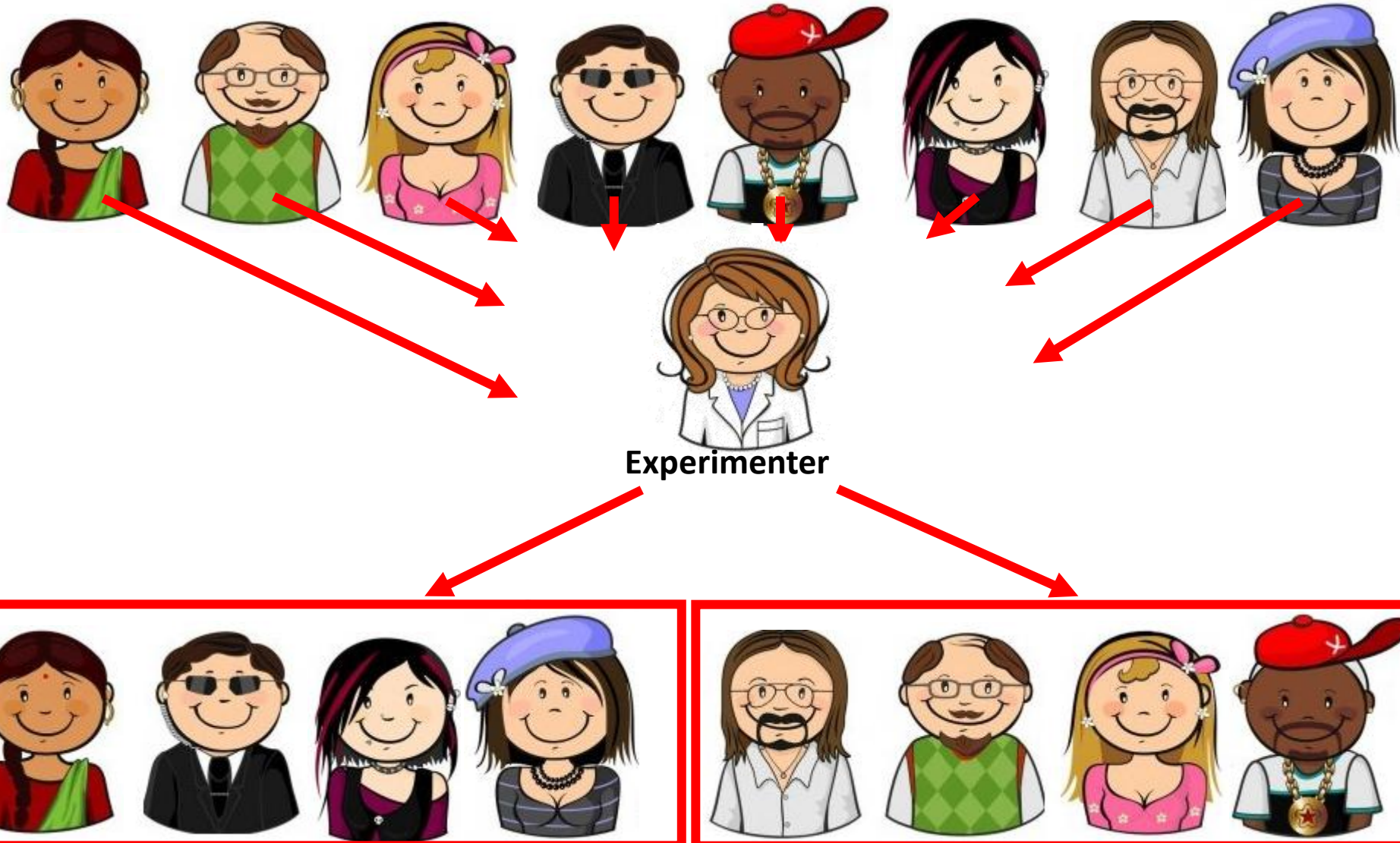
CLASSIFICATION OF CLINICAL TRIALS:
randomized method

Informations about patients

Experimenter

RANDOM

CLASSIFICATION OF CLINICAL TRIALS:
SINGLE-BLINDING
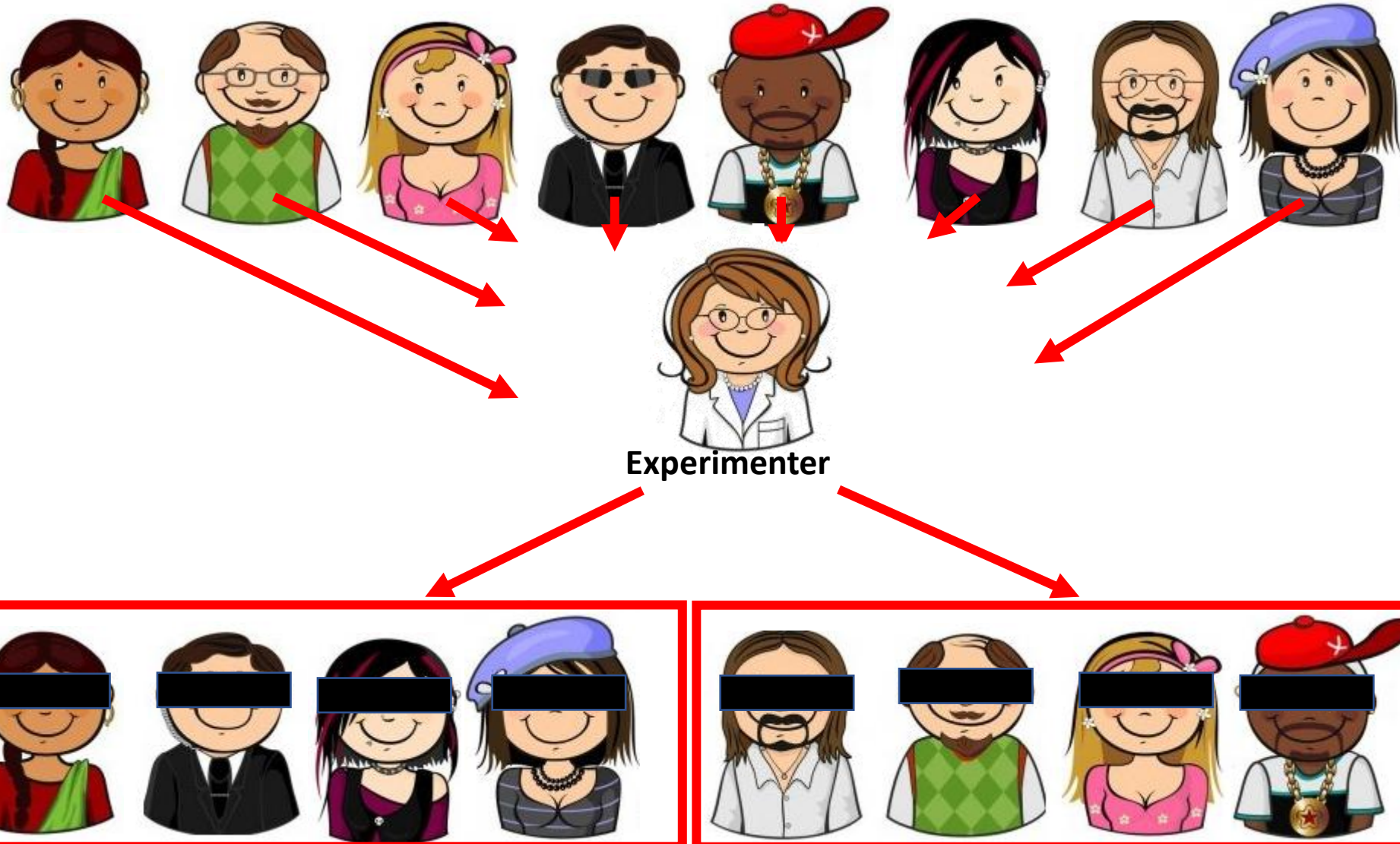
Experimenter

CLASSIFICATION OF CLINICAL TRIALS:
DOUBLE-BLINDING

Experimenter

CLINICAL TRIALS

RANDOMIZATION

GOLD STANDARD:

1) Randomized
2) Double-blind
3) Placebo controlled
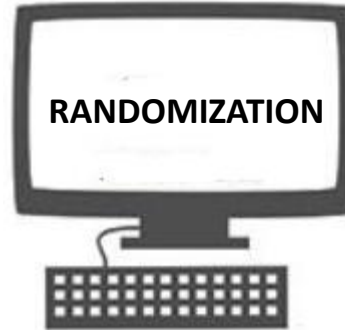
Experimenter
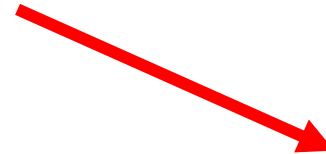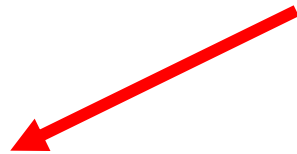
Clinical trial phases

0. Preclinical phase
   1. PHASE I
   2. PHASE II
   3. PHASE III
   4. PHASE IV

PHASE 0 – Discovery and early testing

- Discovery and selection of molecules
- Laboratory analysis on cells and animals
- Administration of extremely small doses of the drug under study to obtain preliminary data on the pharmacokinetics of the agent
- Request for authorization of human trials
- They **do not provide** data on safety and efficacy
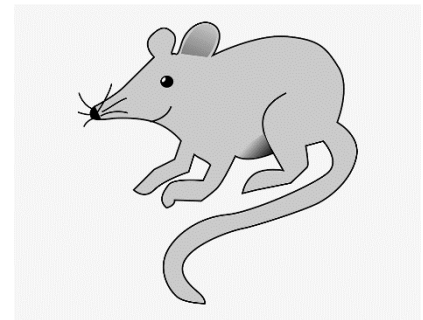
PHASE I – Safety and dosage

- Typically on humans (volunteers) (20-80 subjects)

- Typically on **healthy subjects** (sometimes on terminal patients in the absence of other treatments)

- **It is used to test the pharmacokinetics and toxicity**

- If the safety of the drug has been confirmed, we move on to phase II
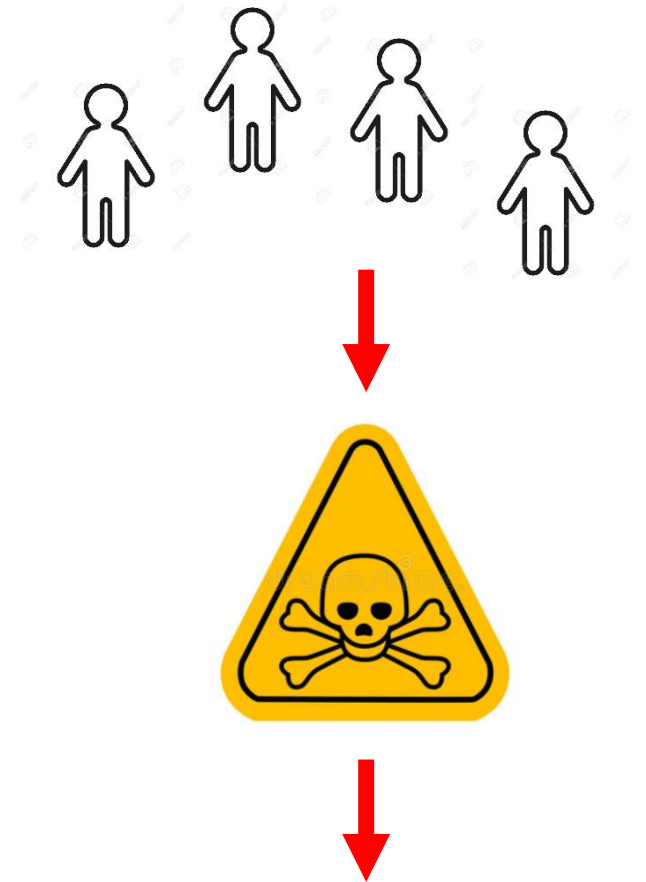
Phase II

PHASE II – Efficacy

- Testing of the molecule on larger groups (300-400 subjects).

- **Patients** who have the pathology for which the particular molecule is to be tested are recruited
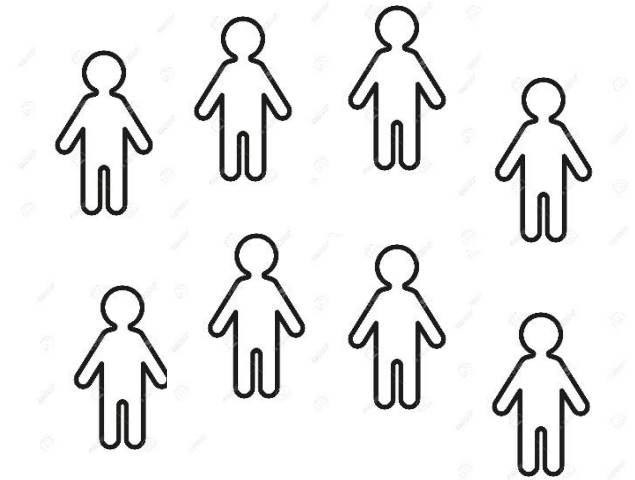
If benefits are observed

Phase III

PHASE III – Approval phase
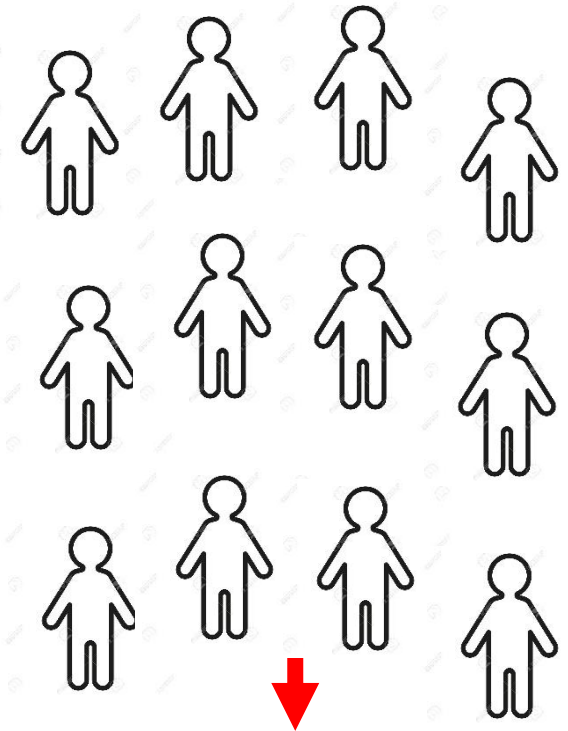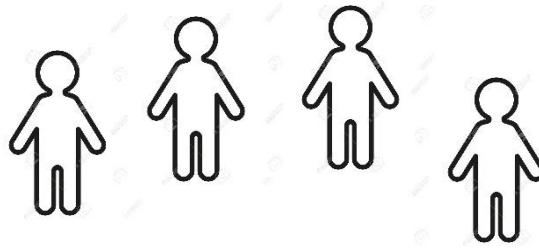
- Increasing the number of patients (multicenter studies with 2000-3000 patients)

- Approval phase

If **few side effects** and **good efficacy**

PHASE IV – Post-marketing surveillance

- MARKET LAUNCH

- Phase that lasts "forever"

- The recording of side effects continues.

- Ex: Thalidomide, marketed after animal testing (late 50s)

→Lancet study

→administration of thalidomide to pregnant mice resulted in the birth of broods with severe limb malformations (phocomelia)

→Recall from the market→Mandatory testing on pregnant animals→compensation to the "victims"
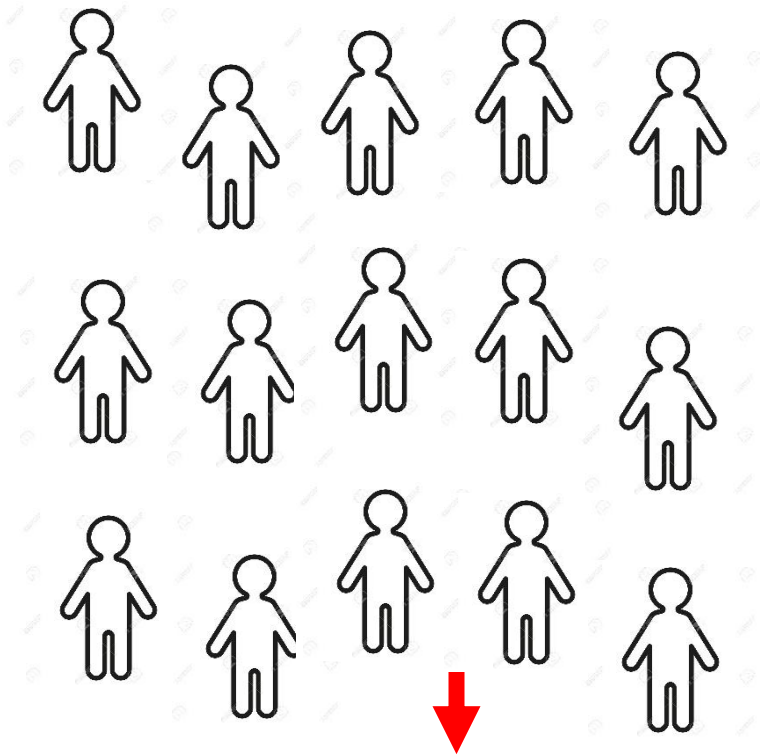
If few side effects and good efficacy

- **STANDARD TRIALS (Phase I, II and III):**

  VERUM GROUP
  (active arm)

  PLACEBO GROUP
  (placebo arm)

- If active arm > placebo arm → We proceed with the other phases of the trial

Gold standard?
All that glitters is not gold

RCTs Problems

PLACEBO IN CLINICAL TRIALS: PROBLEMS

We administer the ACTIVE treatment (active arm) and...
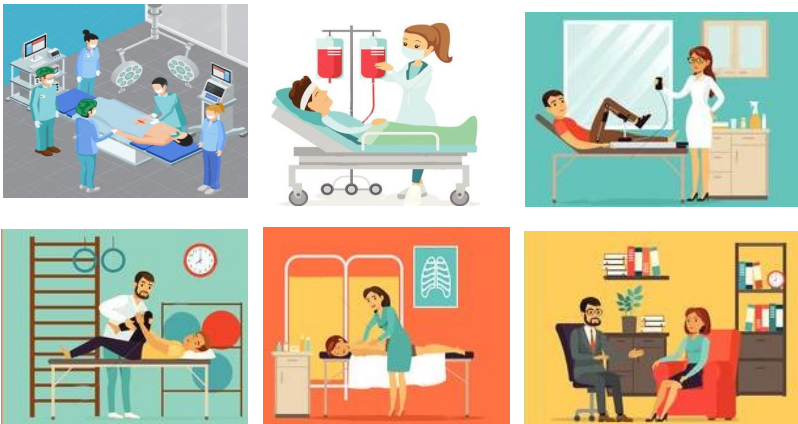
WE COMPARE WITH PLACEBO (placebo arm)

pain

Treatment administration

Treatment efficacy

Natural History (NH)
Regression to the mean
Bias

NON-SPECIFIC FACTORS
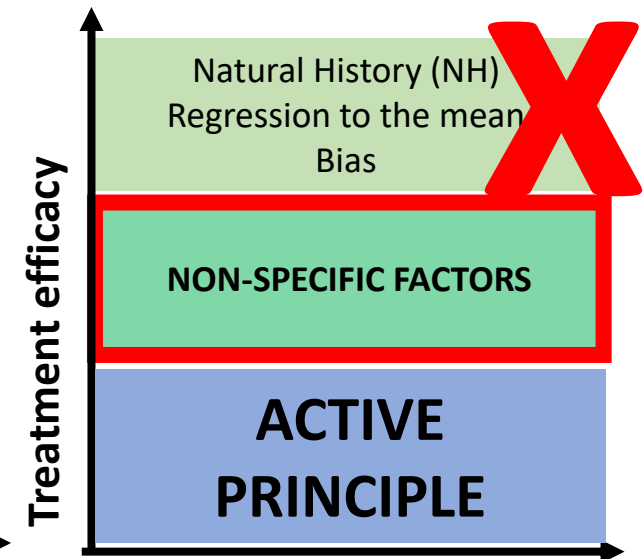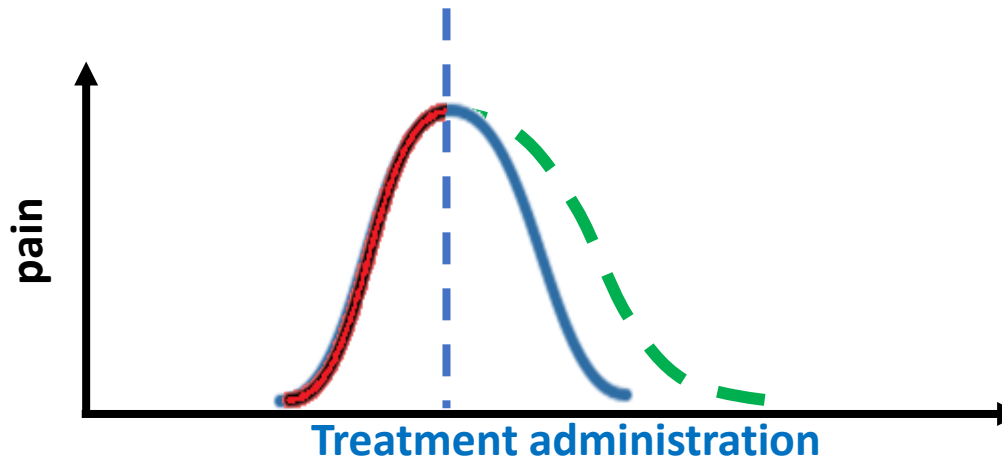
ACTIVE
PRINCIPLE

PLACEBO IN CLINICAL TRIALS: PROBLEMS

One therapy is tested by comparing the **"active treatment arm"** with the **"placebo arm".**

Unfortunately, this comparison often generates uncertainty for several reasons:

- Wrong interpretation (I report a difference that does not exist).
- Inability to find a difference between active treatment and placebo arm
- Increase in negative RCTs over time

Benedetti F, Carlino E, Piedimonte A. Increasing uncertainty in CNS clinical trials: the role of placebo, nocebo, and Hawthorne effects. *Lancet Neurology* 2016.

PLACEBO IN CLINICAL TRIALS: PROBLEMS

Clinical trial: postoperative pain
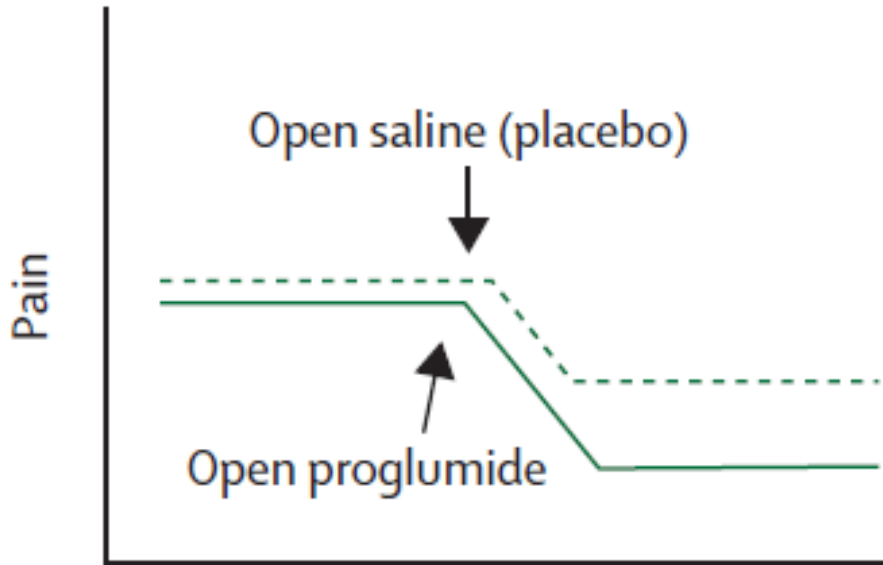
Proglumide (CCK receptor antagonist, solid line) appears to reduce pain more than placebo (dotted line)

→ **Is proglumide a painkiller**??

Benedetti F, Amanzio M, Maggi G. Potentiation of placebo analgesia by proglumide. *Lancet* 1995.
Benedetti F, Carlino E, Piedimonte A. Increasing uncertainty in CNS clinical trials: the role of placebo, nocebo, and Hawthorne effects. *Lancet Neurology* 2016.

PLACEBO IN CLINICAL TRIALS:
ACTIVE ARM PROBLEMS

Clinical trial: postoperative pain

Pain

However, **HIDDEN administration of proglumide** (without the patient's knowledge) has **NO effect on pain perception.** It is no different from placebo.

The explanation is that proglumide does not act as a painkiller but as a **placebo booster (or expectancy booster)**

Hidden saline

Hidden proglumide

Benedetti F, Amanzio M, Maggi G. Potentiation of placebo analgesia by proglumide. *Lancet* 1995.
Benedetti F, Carlino E, Piedimonte A. Increasing uncertainty in CNS clinical trials: the role of placebo, nocebo, and Hawthorne effects. *Lancet Neurology* 2016.

PLACEBO IN CLINICAL TRIALS:
ACTIVE ARM PROBLEMS

Clinical trial: postoperative pain
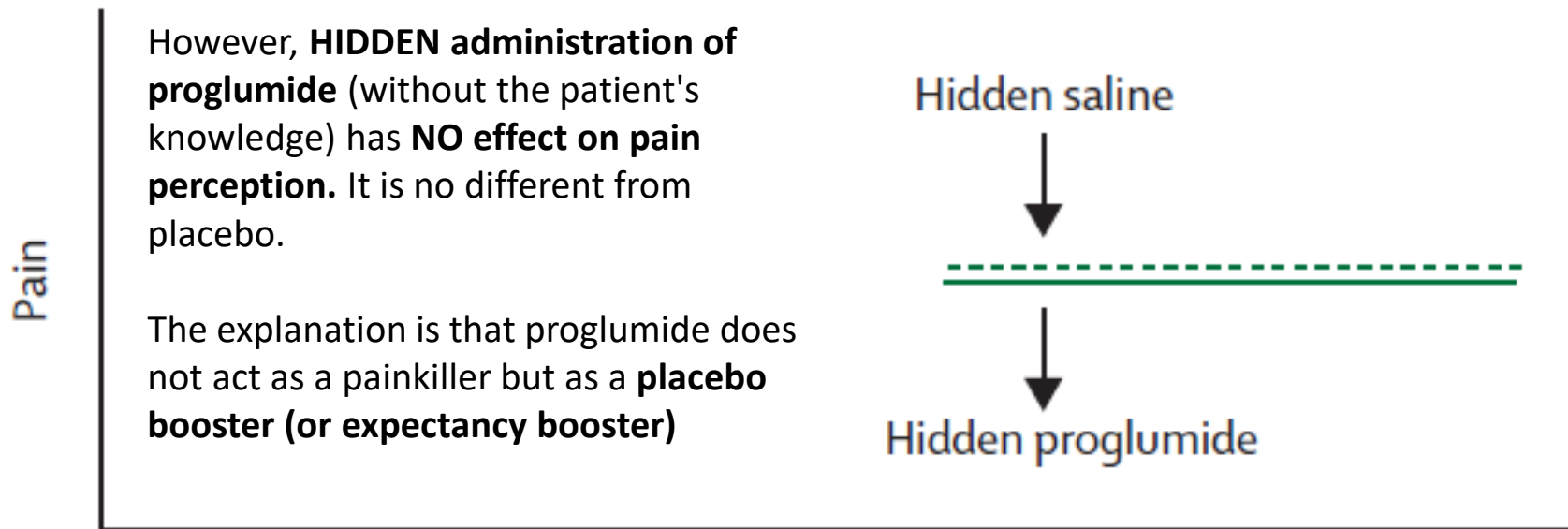
Benedetti F, Amanzio M, Maggi G. Potentiation of placebo analgesia by proglumide. *Lancet* 1995.
Benedetti F, Carlino E, Piedimonte A. Increasing uncertainty in CNS clinical trials: the role of placebo, nocebo, and Hawthorne effects. *Lancet Neurology* 2016.
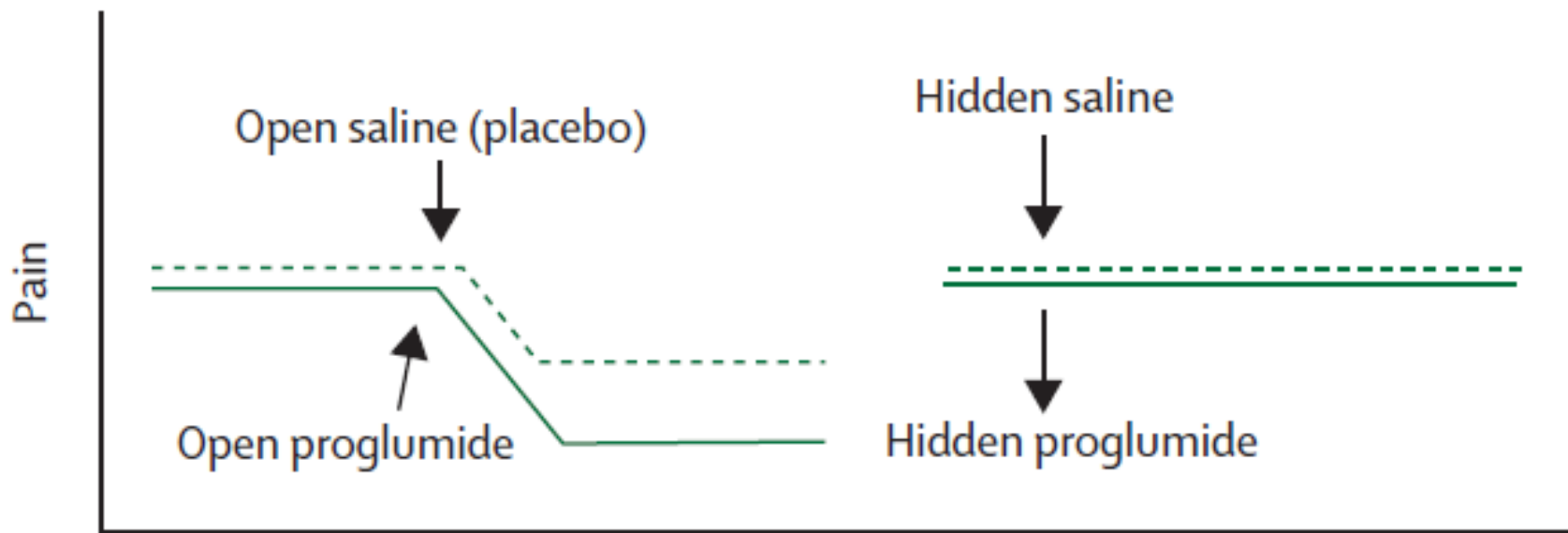
PLACEBO IN CLINICAL TRIALS:
ACTIVE ARM PROBLEMS

Trial of open vs hidden administration of remifentanil (no placebo!)
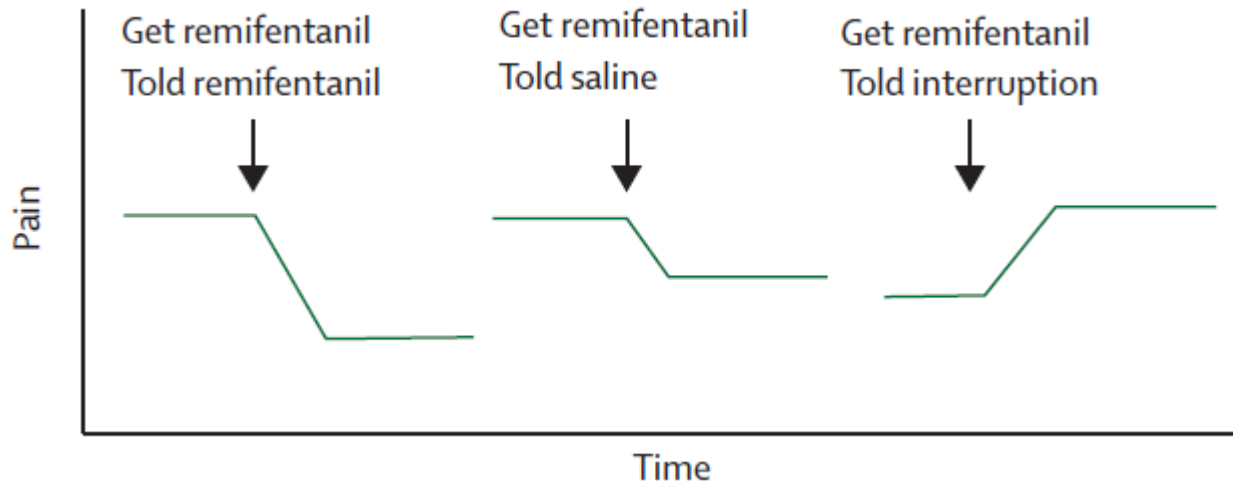
Benedetti F, Carlino E, Piedimonte A. Increasing uncertainty in CNS clinical trials: the role of placebo, nocebo, and Hawthorne effects. *Lancet Neurology* 2016.
Bingel U, Wanigasekera V, Wiech K, et al. The effect of treatment expectation on drug efficacy: imaging the analgesic benefit of the opioid remifentanil. *Sci Transl Med* 2011;

PLACEBO IN CLINICAL TRIALS:
ACTIVE ARM PROBLEMS

- Negative RCTs are increasing over time in different therapeutic areas (oncology, chronic and musculoskeletal pain, CNS disorders)
  - In the majority of trials (52%), the problem is the absence of a difference between the treatment and the placebo→

INEFFICACY

Placebo arm (increase over time) — Active arm (stable over time) — Active arm – Placebo arm (decrease over time)

Carlino E, Vase L. Can knowledge of Placebo and Nocebo Mechanisms Help Improve Randomized Clinical Trials? *Int Rev Neurobiol. 2018*
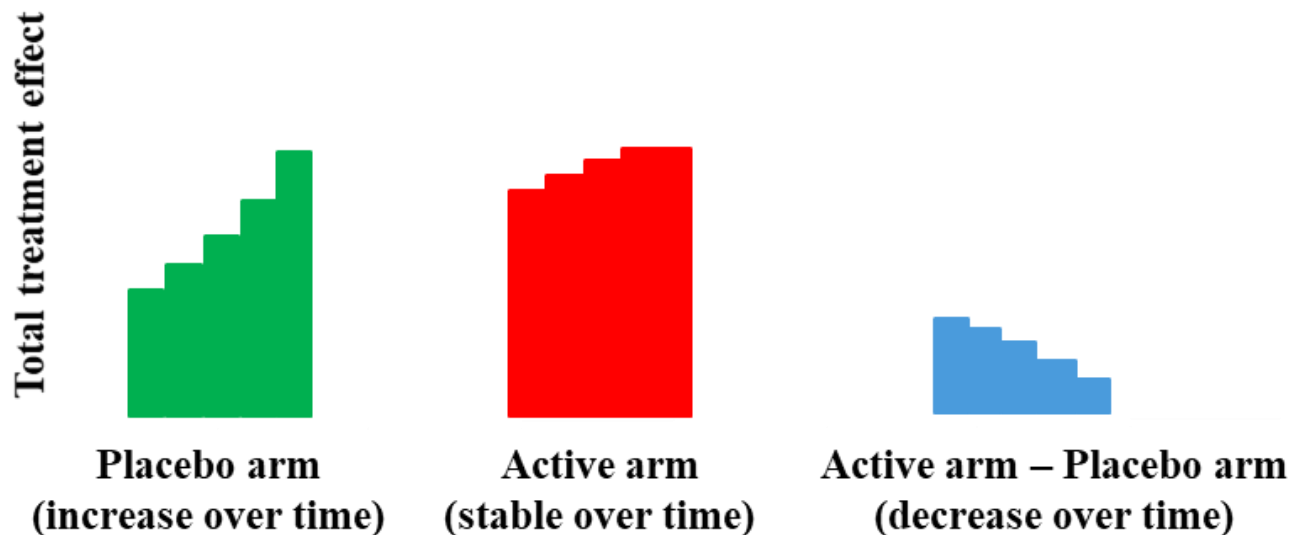
PLACEBO IN CLINICAL TRIALS: ACTIVE ARM PROBLEMS

- Is the placebo effect therefore **increasing**?

- The effect of the **psychosocial context** that accompanies the administration of medical treatment is increasing

| Placebo arm (increase over time) | Active arm (stable over time) | Active arm – Placebo arm (decrease over time) |

Carlino E, Vase L. Can knowledge of Placebo and Nocebo Mechanisms Help Improve Randomized Clinical Trials? *Int Rev Neurobiol. 2018*
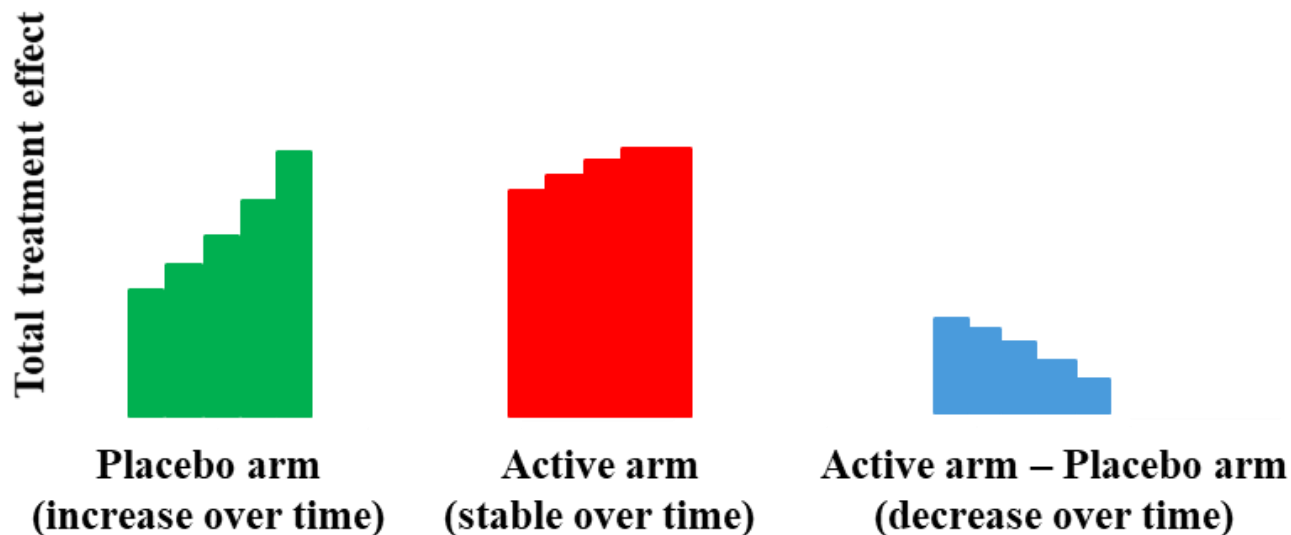
PLACEBO EFFECT = CONTEXT EFFECT

Expectation

Patient characteristics

Previous experience

ASPIRINA

- **VERBAL INFORMATION**
- **DOCTOR-PATIENT RELATIONSHIP**

- **PHYSICAL CONTEXT**
- **PHYSICALITY OF THE TREATMENT**

PLACEBO EFFECT = CONTEXT EFFECT
The placebo effect is the effect of the context

Expectation

Patient characteristics

Previous experience

PLACEBO

- VERBAL INFORMATION
- DOCTOR-PATIENT RELATIONSHIP

- PHYSICAL CONTEXT
- PHYSICALITY OF THE TREATMENT
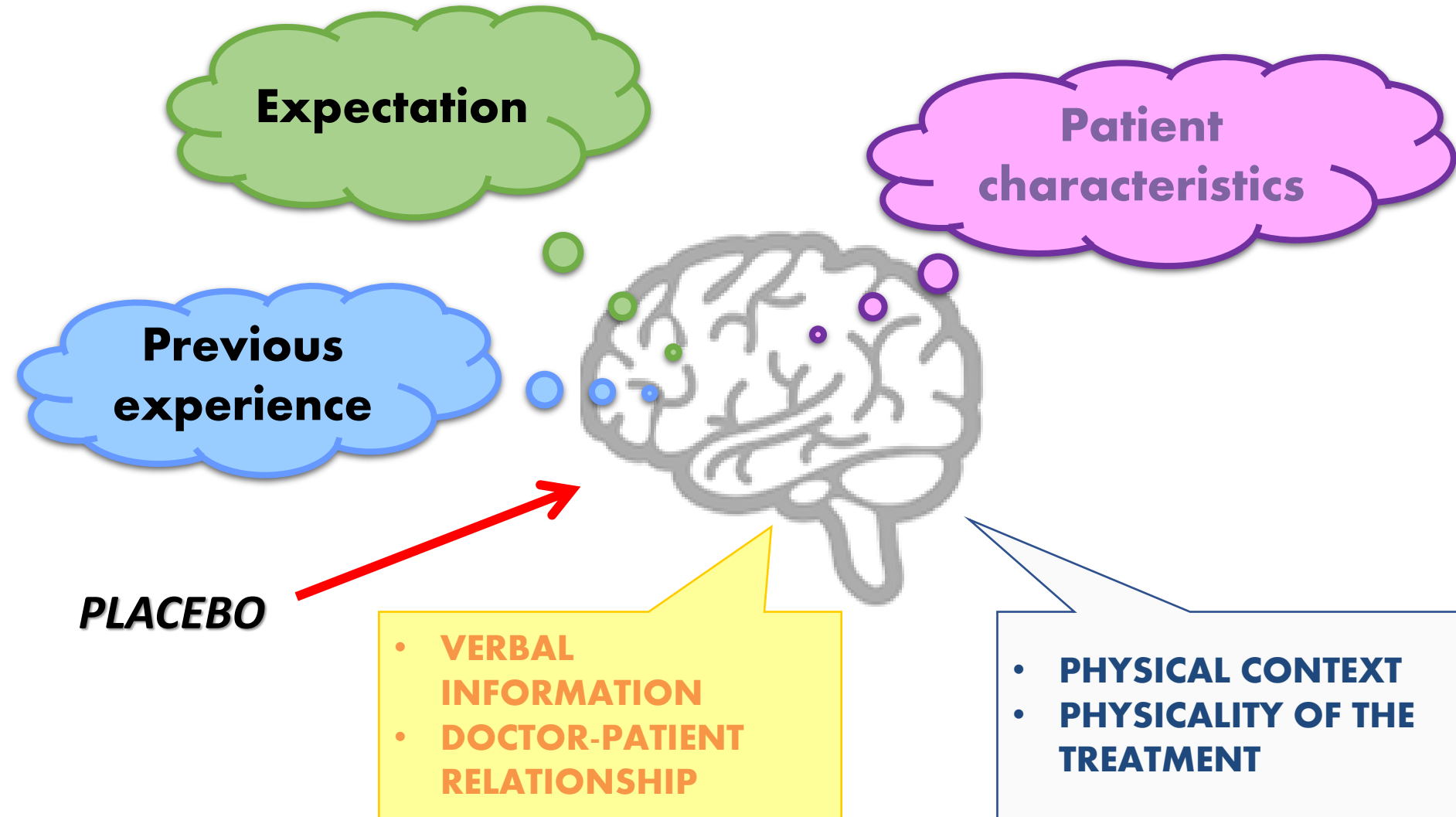
PLACEBO

+ CONTEXT

Inert treatment administered within a psychosocial setting (context effect)
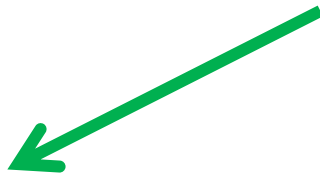
Placebo effect
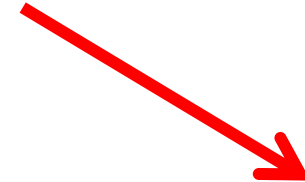
Nocebo effect

Placebo effect ≠ placebo response (RCTs)

Benedetti F, Carlino E, Pollo A. *Neuropsychopharmacology* 2011;36:339-54
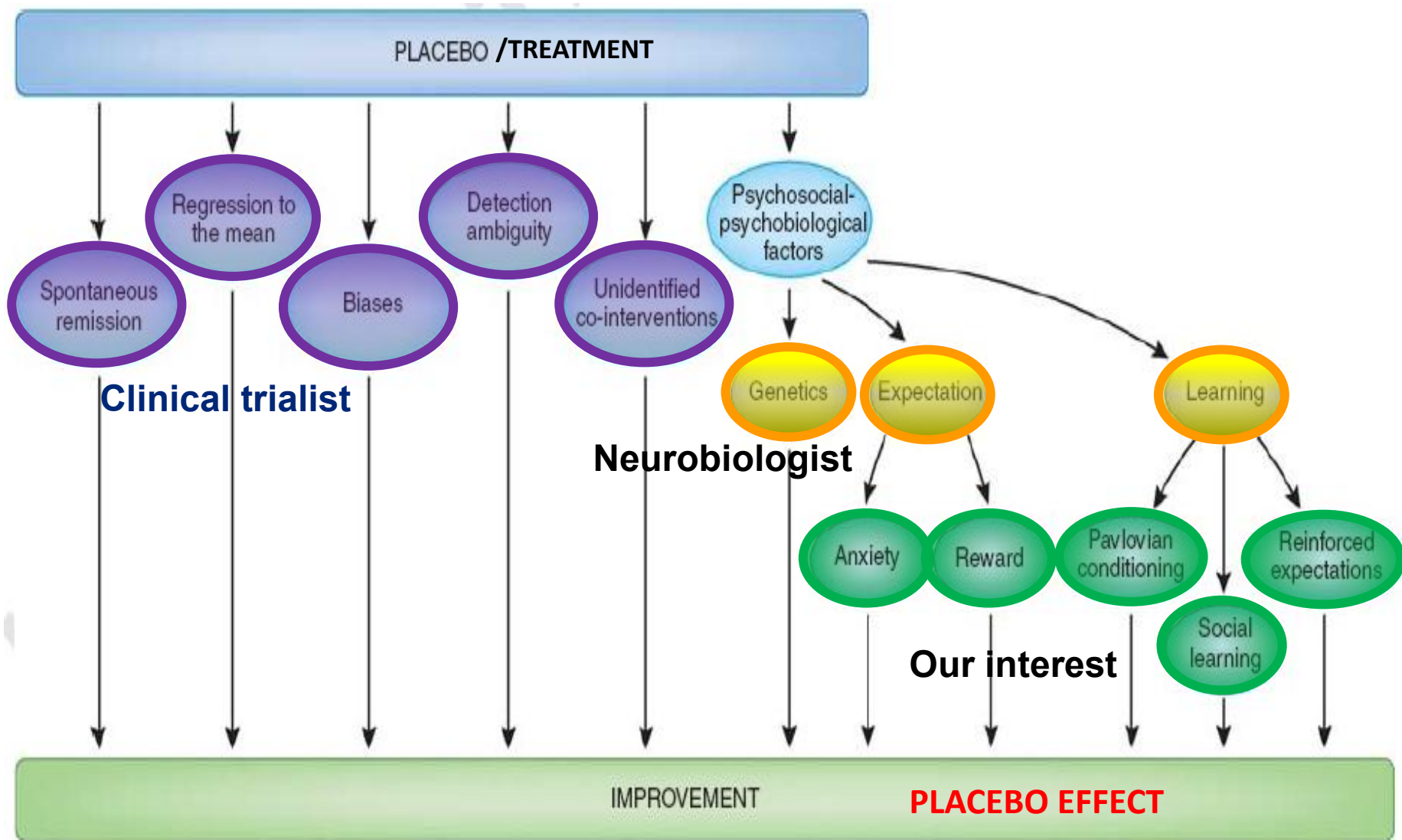
CONTEXTUAL FACTORS:
what are they and how have they been studied?
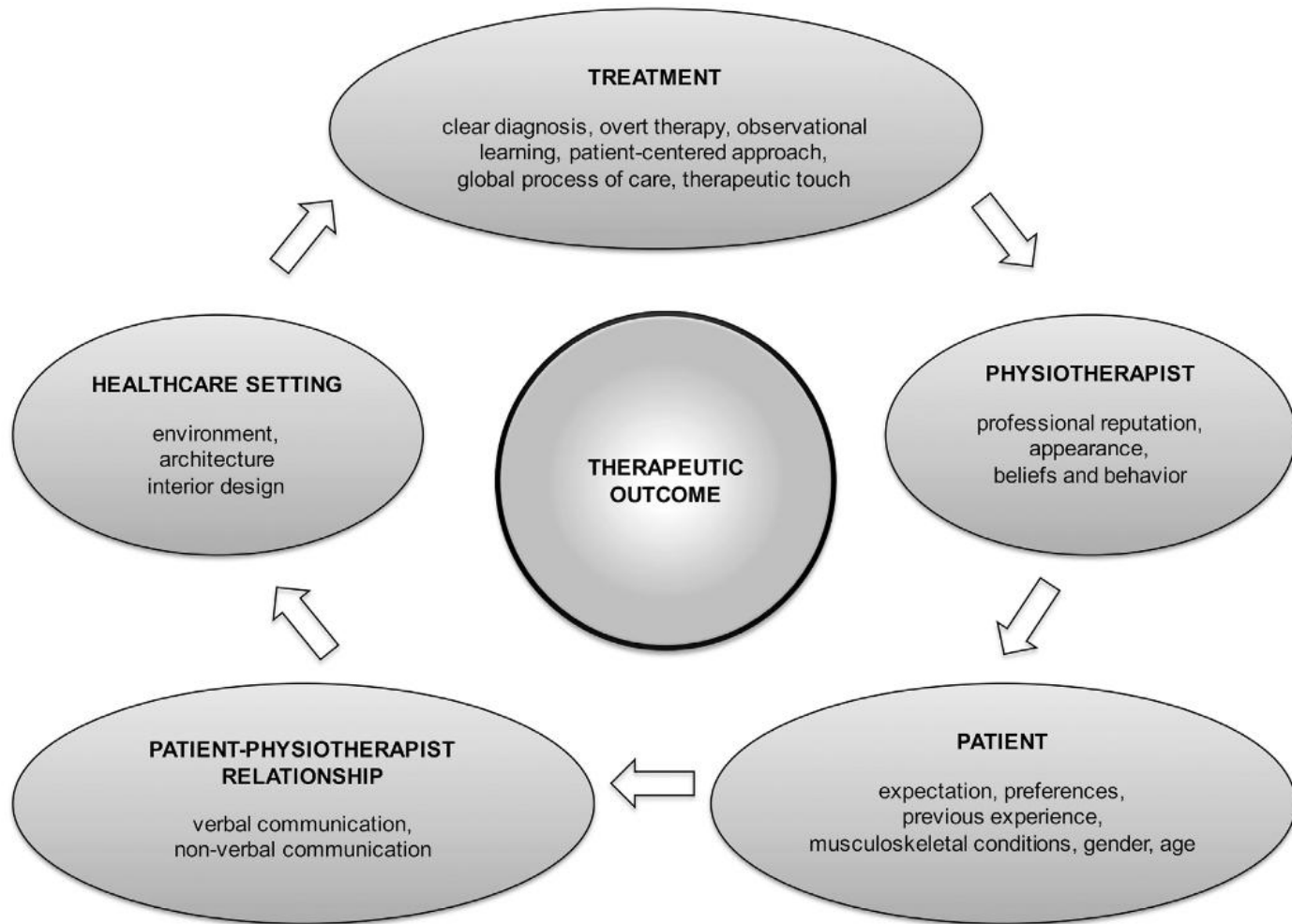
Fig. 3. The contextual factors as modulators of therapeutic outcome.

Testa & Rossettini, 2016, Manual Therapy
Rossettini, Carlino, Testa, 2018, BMC Musculoskeletal Disorders

CONTEXTUAL FACTORS:
what are they and how have they been studied?

Therapeutic outcome is influenced by:

1.PATIENT'S INVIDUAL VARIABLES:

- **Psychological variables:** patients who respond well to placebo (responders) tend to be less anxious and more optimistic
- **Genetic variables:** studies have shown that certain genetic profiles respond better to contextual factors than others.

  → A PET study found a reduction in amygdala activity only in subjects with a specific serotonergic variant (only in subjects **homozygous for the long allele** (5-HTTPLR)) or **the G variant of the G-703T polymorphism** (→ placebo treatment for anxiety)

  → The same has been observed in depressed patients, where individuals with **particular monoamine typologies respond better to certain contexts** (poor response in G and G/G and Met-Met)

- The simple act of administering a treatment can **trigger expectations**
- Exposure to the **therapeutic setting**
- Verbal or non-verbal **interaction**
- **Past medical history**

Furmark et al. (2008) *J. Neurosci*
Leuchter et al. (2009) *J Clin Psychopharmacol*

CONTEXTUAL FACTORS:
what are they and how have they been studied?

Therapeutic outcome is influenced by:

2.PHYSIOTHERAPIST:

- A doctor who presents himself as **competent**, **experienced**, polite, **professional**, **trustworthy**, **able to provide a clear diagnosis** and a **clear prognosis** and who monitors the patient with adequate follow-up, can modulate the patient's symptom by virtue of his or her behavior.

- It has been shown that the **information and opinion of the physician regarding the clinical pathway**, regarding the therapy and the prognosis→ influence therapeutic outcome

- **Nonverbal communication** plays a huge role

- The use of **Therapeutic Touch** can have an impact on the patient's symptom

- **In addition to verbal and non-verbal communication, touch is the third modality involved**

 → **a powerful emotionally important somatosensoty stimulus is represented by holding hands (social support and affection)**
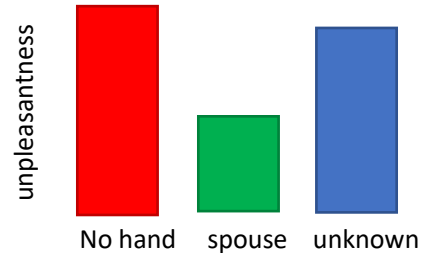
Testa & Rossettini, 2016, Manual Therapy
Rossettini, Carlino, Testa, 2015, BMC Musculoskeletal Disorders
Lu et al., 2013, Geriatric Nursing

NON-THERAPEUTIC TOUCH

→ fMRI study on the biological effect of holding hands

→ Married women were exposed to the threat of an electric shock under three conditions:

→ **not holding hands**/**spouse hand**/**stranger hand**

When they **held their spouse's hand**, they reported **less unpleasantness** and showed **reduced activation** in brain regions involved in processing emotional and behavioral responses to threat, specifically the **dorsolateral prefrontal cortex (DLPFC)**, **nucleus accumbens**, and **colliculus**.

Here was also **reduced activation** in the **ventral anterior cingulate cortex (vACC)**, **posterior cingulate**, **postcentral gyrus**, and **supramarginal gyrus** when holding the hand of **either their spouse or a stranger**

THERAPEUTIC TOUCH

→ The effect of healing touch on the pain and mobility in patients with osteoarthritis (OA)

→ Randomized-control trial, patients with OA

→2 different treatments + standard treatment: Healing touch session 3 times a week for 6 weeks or weekly friendly visits (FV)

→Pain intensity measures and joint mobility measures
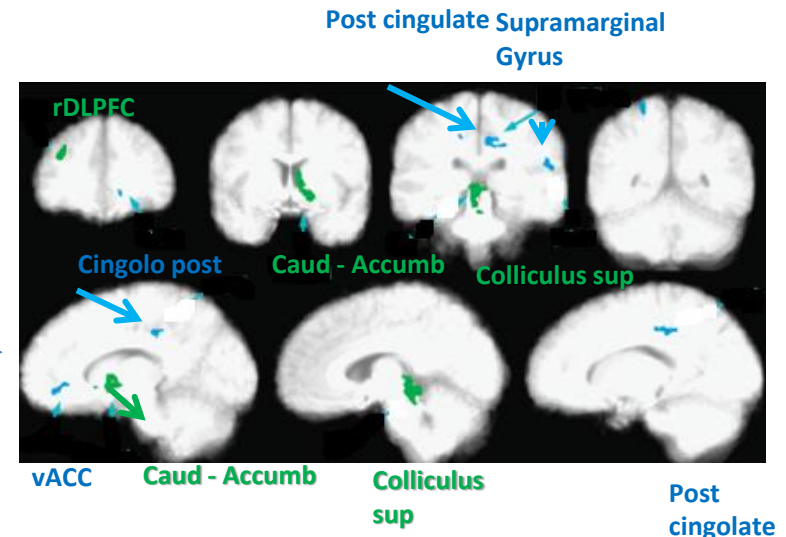
Lu et al., 2013, Geriatric Nursing
Coan et al., 2007, Psychological Science

CONTEXTUAL FACTORS:
what are they and how have they been studied?

Therapeutic outcome is influenced by:

3.TREATMENT:

- The formulation of a **clear diagnosis** that explains the symptoms to the patient and gives meaning to the disease is in fact a form of treatment (Hopayian and Notley, 2014)

- Detailed diagnoses and comprehensive explanations are appreciated by the patient→ Increased satisfaction→ Therapeutic adherence (Hush et al., 2011; Ludvigsson andEnthoven, 2012; Pinto et al., 2012)

- **Patient-centered treatment**

- Organizational aspects→ same therapist, clarity, adequate length of sessions, punctuality, flexibility, frequency and duration of follow-ups→ increase patient satisfaction → better outcome

Testa & Rossettini, 2016, Manual Therapy
Rossettini, Carlino, Testa, 2018, BMC Musculoskeletal Disorders

CONTEXTUAL FACTORS:
what are they and how have they been studied?

Therapeutic outcome is influenced by:

4.PATIENT-PHYSIOTHERAPIST RELATIONSHIP:

- **Appropriate verbal communication** is a prerequisite for a good therapeutic relationship (Parson et al., 2007).

- **Supportive verbal expressions, active listening, encouragement, empathy** correlate with patient satisfaction and can influence therapeutic outcome (Hush et al., 2011; Oliveira et al., 2012; Pinto et al., 2012;O'Keeffe et al., 2015)

- Patients not satisfied with interruptions, lack of empathy and arrogance (O'Keeffe et al., 2015)

- Facial expressions and eye contact are crucial therapeutic means (Pinto et al., 2012) since they bring important "meanings" to the patient (Benedetti, 2013)

- Facial expressions change the processing of pain stimuli (Wieser et al., 2014) and modulate placebo analgesia (Valentini et al., 2014).

- Gestures, postures, and physical contact add meaning to verbal interaction (Josephson et al., 2015; O'Keeffe et al., 2015).

HOW TO GIVE INFORMATION

Augmented group:
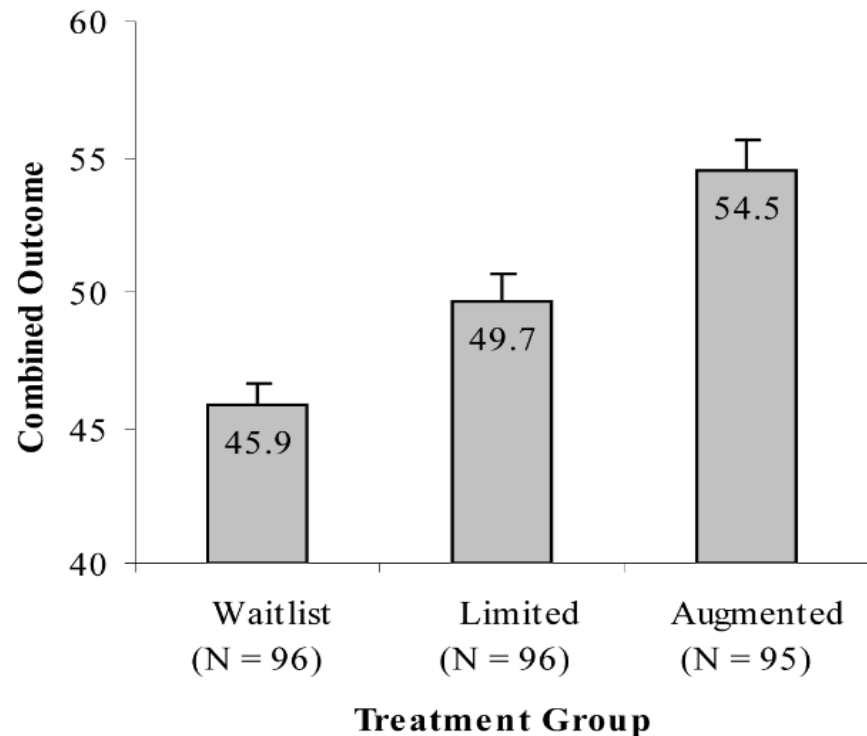Treated with an empathetic approach

Limited group:
Treated with a neutral approach

Control group

- IBS patients
- Placebo acupuncture

Kelley et al., Psychosom Med. 2009

CONTEXTUAL FACTORS:
what are they and how have they been studied?
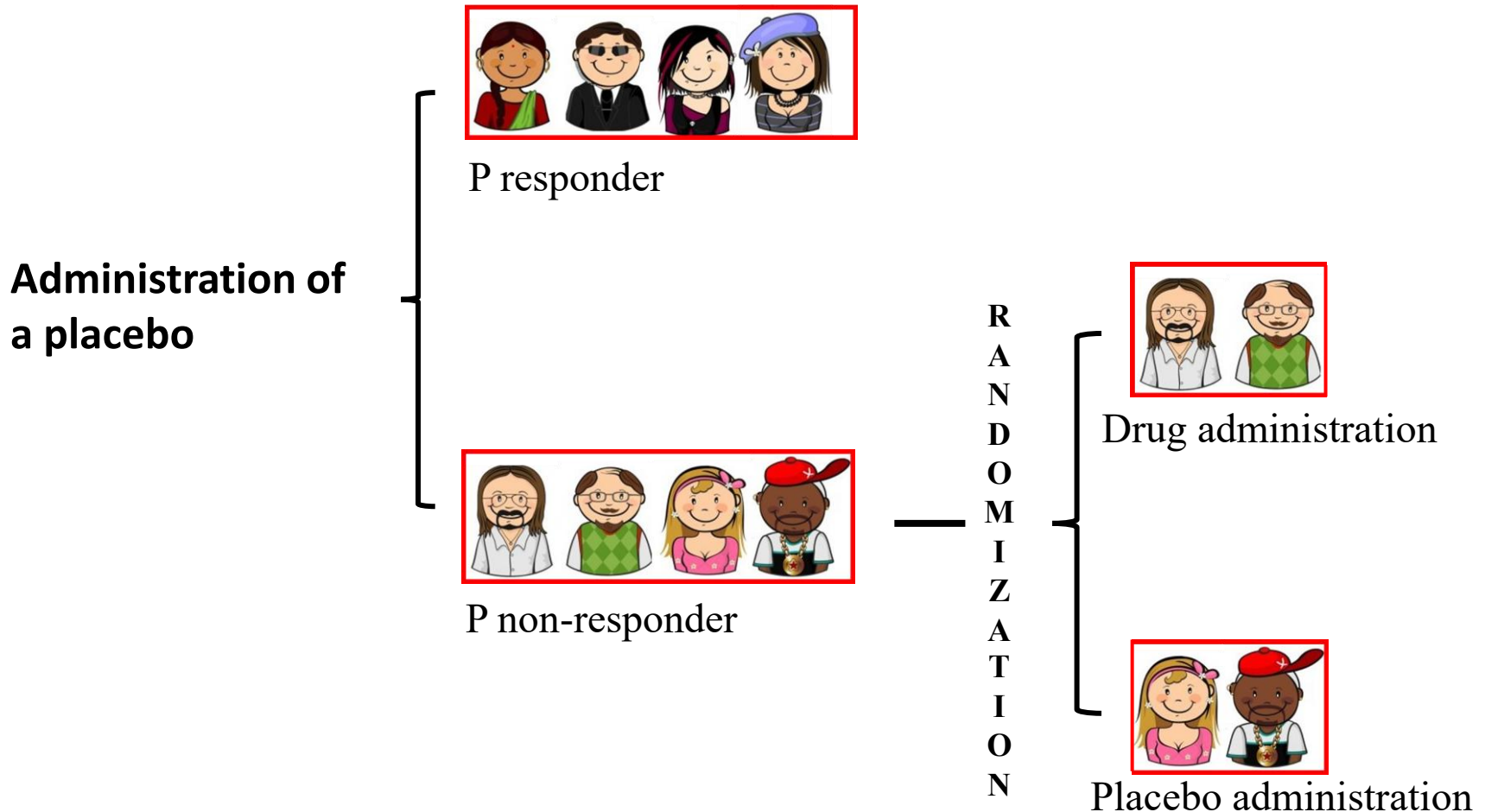
Table 2
Strategies to enhance placebo in physiotherapy.

Key points

Physiotherapist's and patient's features
- Improve professionalism, reputation, training and expertise;
- Use a laboratory coat or tailored clothing;
- Be optimistic during the consultation and regarding the dysfunction;
- Deliver clear diagnosis, prognosis and explanation of the patient's problem;
- Explore the patient's disease and illness, request and trust the patient's opinion;
- Encourage questions, answer queries from the patient, deliver positive feedback;
- Investigate expectation, preferences and the patient's previous experiences;
- Consider the phase of the musculoskeletal condition, gender and age of the patient;

Patient-physiotherapist relationship
- Be warm, confident, friendly, relaxed and open during the clinical encounter
- Use verbal expressions of empathy, support, sympathy and language reciprocity;
- Adopt psychosocial talk, partnership statements and paraphrase;
- Use positive messages associated with treatment for pain relief;
- Use eye contact, smiling, caring expressions of support and interest;
- Use affirmative head nodding, forward leaning and open body posture;
- Interpret patient's nonverbal body language expressions;

Treatment features
- Use open treatment, show and tell the patient that a therapy is applied;
- Boost the patient's willingness to talk to other patients who undergo the same treatment with positive results;
- Use patient-centred care, personalize the treatment;
- Deliver the treatment by the same physiotherapist in a clean and private environment,
- Set appointments with adequate length, punctuality, frequency, follow-up;
- Use touch to assist, prepare, inform, care of, perceive and treat patients;

Healthcare setting features
- Combine positive distractors as light, music, temperature and aromas,
- Adopt supportive indications to facilitate access to physiotherapy service;
- Decorate the therapeutic environment with artworks and ornaments;

Testa & Rossettini, 2016, Manual Therapy
Rossettini, Carlino, Testa, 2018, BMC Musculoskeletal Disorders

TYPES OF CLINICAL TRIAL
Placebo run-in
→EXCLUDING PLACEBO RESPONDERS

P responder

Administration of a placebo

P non-responder

R A N D O M I Z A T I O N

Drug administration

Placebo administration

Active run-in →
EXCLUDE SUBJECTS WHO DO NOT RESPOND TO THE DRUG

Administration of a drug

- F non-responder o
- Marked collateral effect

- F responder
- Few side effects

RANDOMIZATION
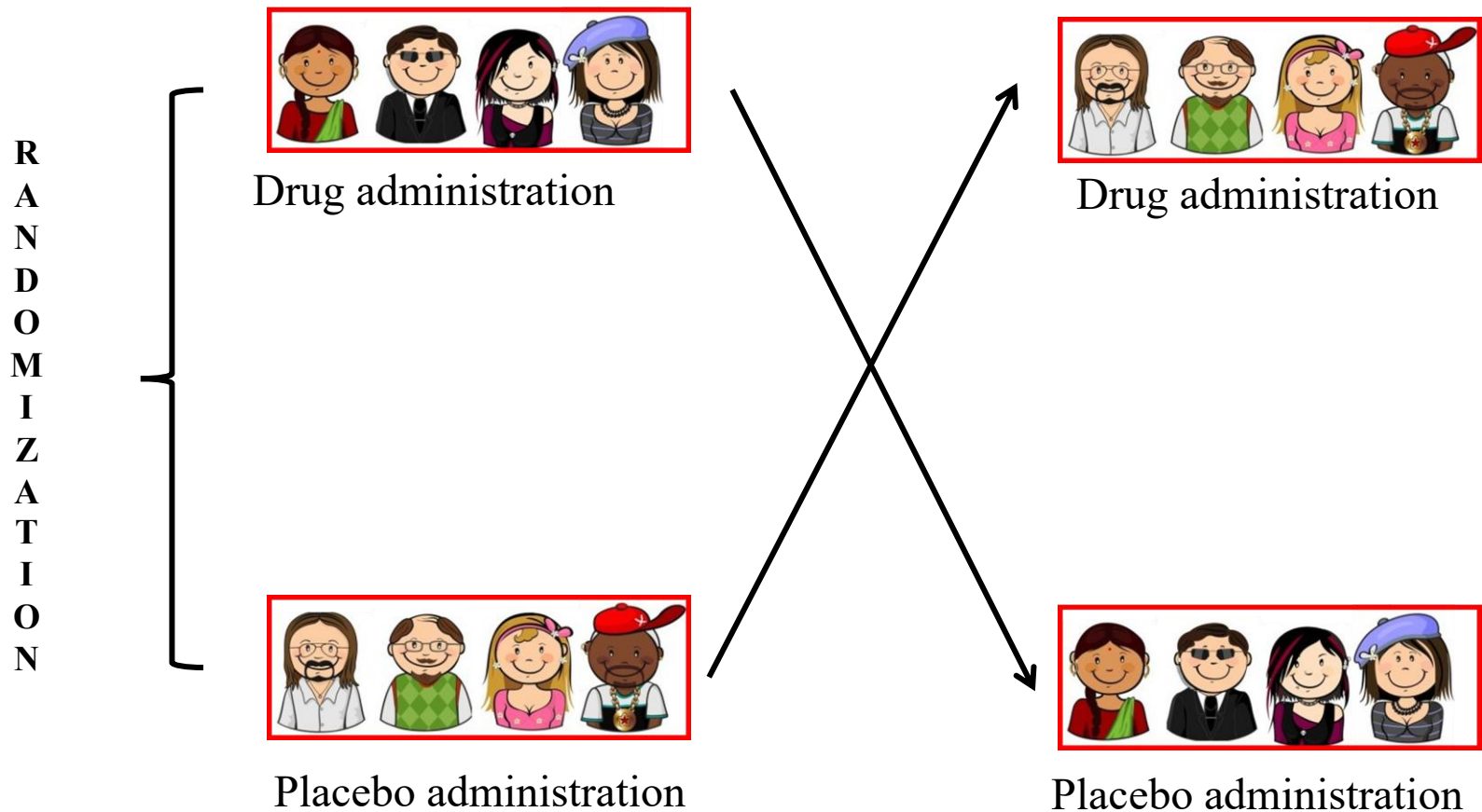

Drug administration

Placebo administration

CROSS-OVER DESIGN

R
A
N
D
O
M
I
Z
A
T
I
O
N

Drug administration

Drug administration

Placebo administration

Placebo administration

TRIAL BASED ON ASSIGNMENT
(real or perceived)

REAL ASSIGNMENT

ASSIGNMENT RECEIVED

Placebo administration

Placebo administration

RANDOMIZATION

**"What group
do you think
you belong to?"**

Drug administration

Drug administration

or Latin-squared design

BALANCED DESIGN

GET

|	MEDICATION	PLACEBO
MEDICATION	ACTIVE + Placebo	PLACEBO EFFECT
PLACEBO	ACTIVE EFFECT	BASELINE

TOLD

ETHICAL ISSUES IN THE USE OF PLACEBO

- Use of placebo prohibited dentologically in certain conditions (e.g. depression, suicide risk, patients with cancer, etc.).

- Without the placebo group, is it possible to evaluate the efficacy of a treatment?

- Possible use of trials with two active drugs (Old vs New) to evaluate the efficacy of the drug.

- Possible use of open-hidden trials.

OPEN-HIDDEN

OPEN
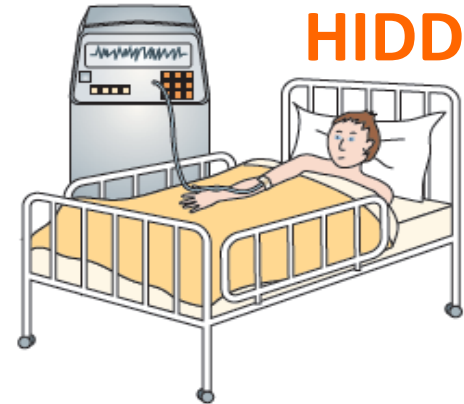
HIDDEN

- Participants **know they are receiving the tratment**
- Allows both **pharmacological effects** and **psychological/placebo effects** to occur

- Participants **don't know when or if** they receive the treatment
- **Isolates the pure pharmacological effect** by removing expectation or placebo influence
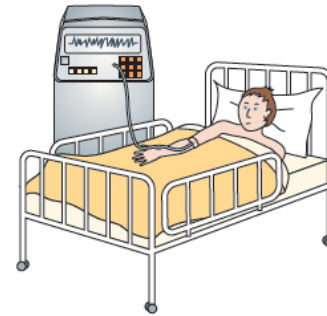
Enck et al, 2013, Nature 12:191-204.
Benedetti F, Carlino E, Pollo A. 2011 Clin Pharm Ther 90: 651-661.

OPEN-HIDDEN

Is metamizol (300 mg) effective in post-operative pain?
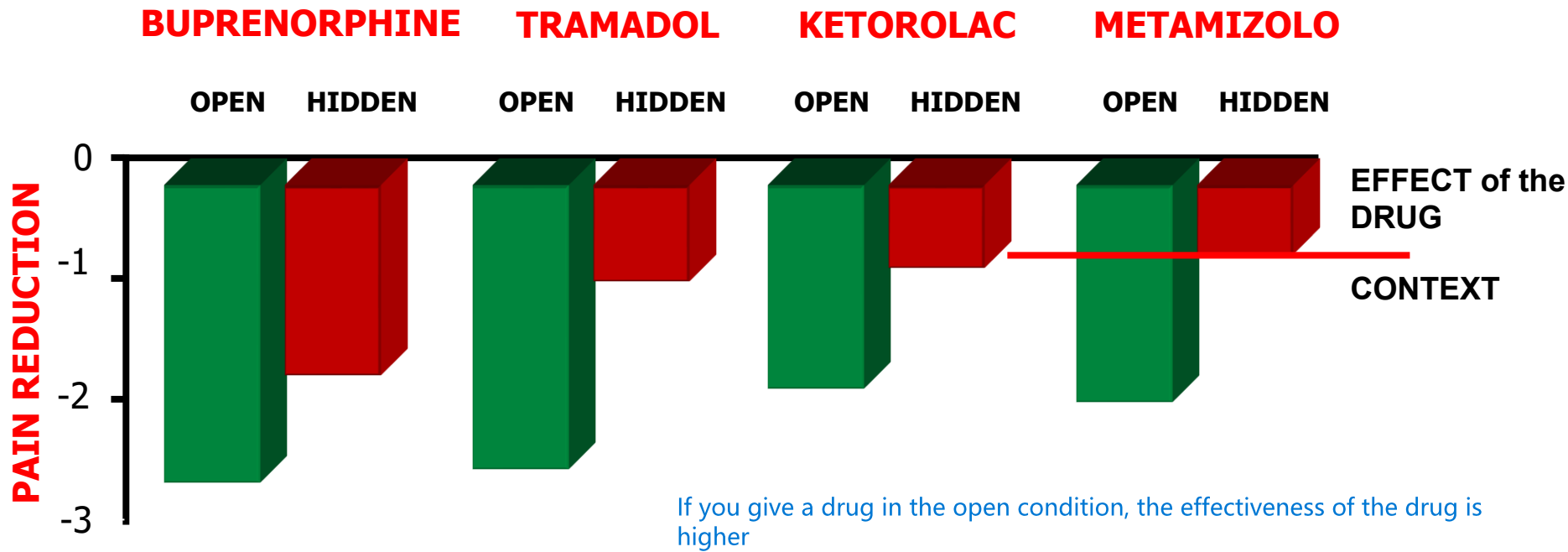**Double blind**

Open group (N=10)

Hidden group (N=10)

Informed consent "You will receive a dose of metamizole but you will not know when"

Colloca and Benedetti, *Nature Rev Neurosci* **6: 545-552, 2005**

OPEN-HIDDEN

Benedetti *et a*l. 1995 *Lancet* 346: 1231;
Amanzio *et al.* 2001 *Pain* **90**: 205-15;
Colloca *et al.* 2004 *Lancet Neurol 3: 679-684*

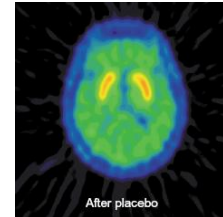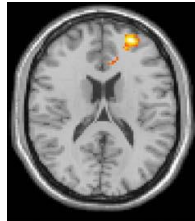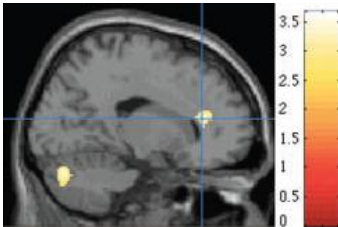# Placebo, nocebo and contextual factors:

history, research and clinical practice

PLACEBO in modern science: 3 contexts

- **In clinical trials → the aim is to REDUCE the placebo effect**

- **In scientific research → the aim is to UNDERSTAND how the placebo effect works**

- **In clinical practice → the aim is to INCREASE the placebo effect**

PLACEBO in modern science: SCIENTIFIC RESEARCH

Under what conditions does it work?

How can it be studied?

How much does it work?

How does that work:
1) Psychological mechanisms
2) Neurobiological mechanisms

- **In research→ UNDERSTAND**

After placebo
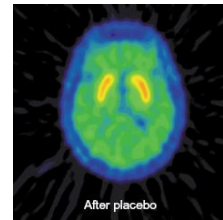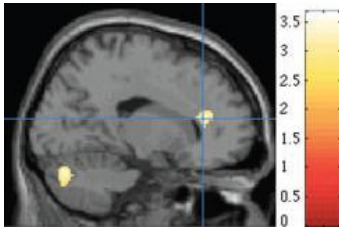
Who does it work on?
On what population?

Under what conditions does it work?

Pain

Motor performance

Parkinson's disease

Alzheimer's disease

Cardiovascular system

Respiratory system

Gastrointestinal System

Immune system

Endocrine system

Depression

Anxiety

Finniss et al. *Lancet* 2010;375:686-95

How can it be studied?

BEHAVIORAL STUDIES
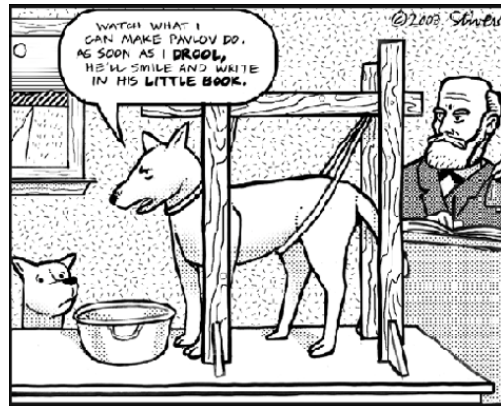
fMRI / PET
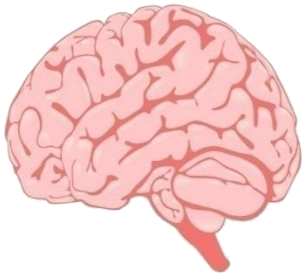
PHARMACOLOGY

EEG

Magnitude of the placebo effect

- Several studies have measured and quantified the **magnitude of the placebo/nocebo effect induced by contextual factors under different conditions.**

E.g. Musculoskeletal pain, fibromyalgia, osteoarthritis (effect size > 0.5)

Proportion of Treatment Effects

Rossettini, Carlino, Testa, 2015, BMC Musculoskeletal Disorders
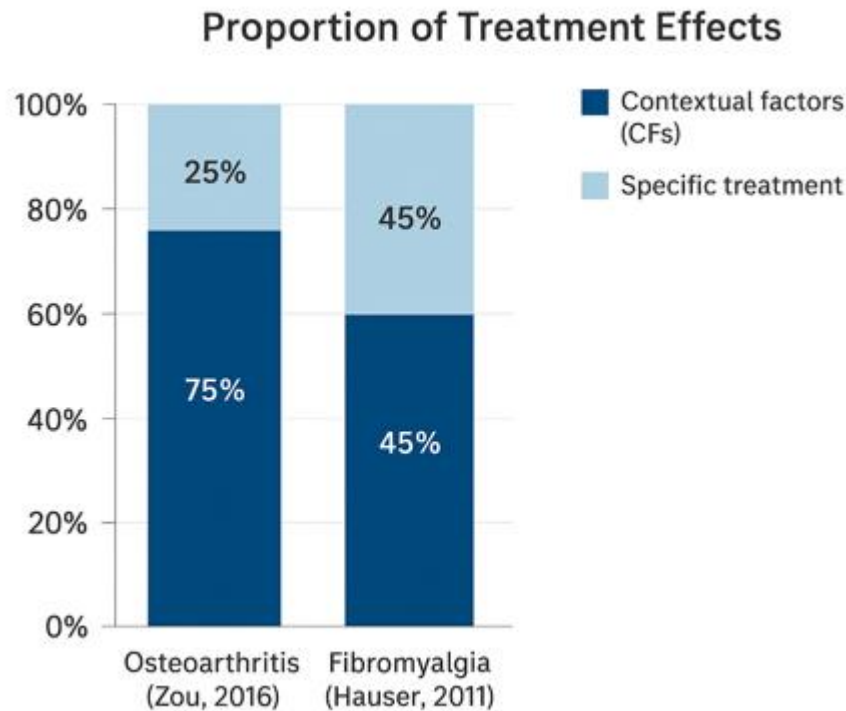
PSYCHOLOGICAL MECHANISMS

- Theoretical aspects:
  - **Expectation: Models**
    - Pierce's theory → SIGNS
    - Atkinson → EXPECTATIONS + SUBJECTIVE VALUE
    - Khaneman, Tversky → PROSPECT THEORY (loss and gain)
    - Rescorla-Wagner → ASSOCIATIVE LEARNING PROCESS
    - ViolEx Model → VIOLATION OF EXPECTATION
    - Bayesian perspective → PRIORS AND SENSORY INPUTS
  - **Conditioning:**
    - Classical
    - Operant
    - Social

- From theory to practice: placebo effect studies

Expectation

"Placebo interventions, such as sugar pills or saline injections, can be vehicles of therapeutic responses, but not by virtue of containing medication or internal properties with the power to produce beneficial health outcomes. Instead, the placebo intervention—a placebo pill, saline injection, and the invasive procedure or device that works by virtue of the placebo effect—should be understood as **a signal, or set of signals, which convey information**"

context →

context → **EXPECTATIONS** → **PLACEBO EFFECT**

context →

Colloca & Miller, 2003

Expectation: different theories

Peirce Theory

Atkinson's expectancy-value

Rescorla-Wagner's model

Expectations

Kahneman and Tversky

Bayesian Brain

Rief model (Viol-EX)

Colloca & Miller, 2003
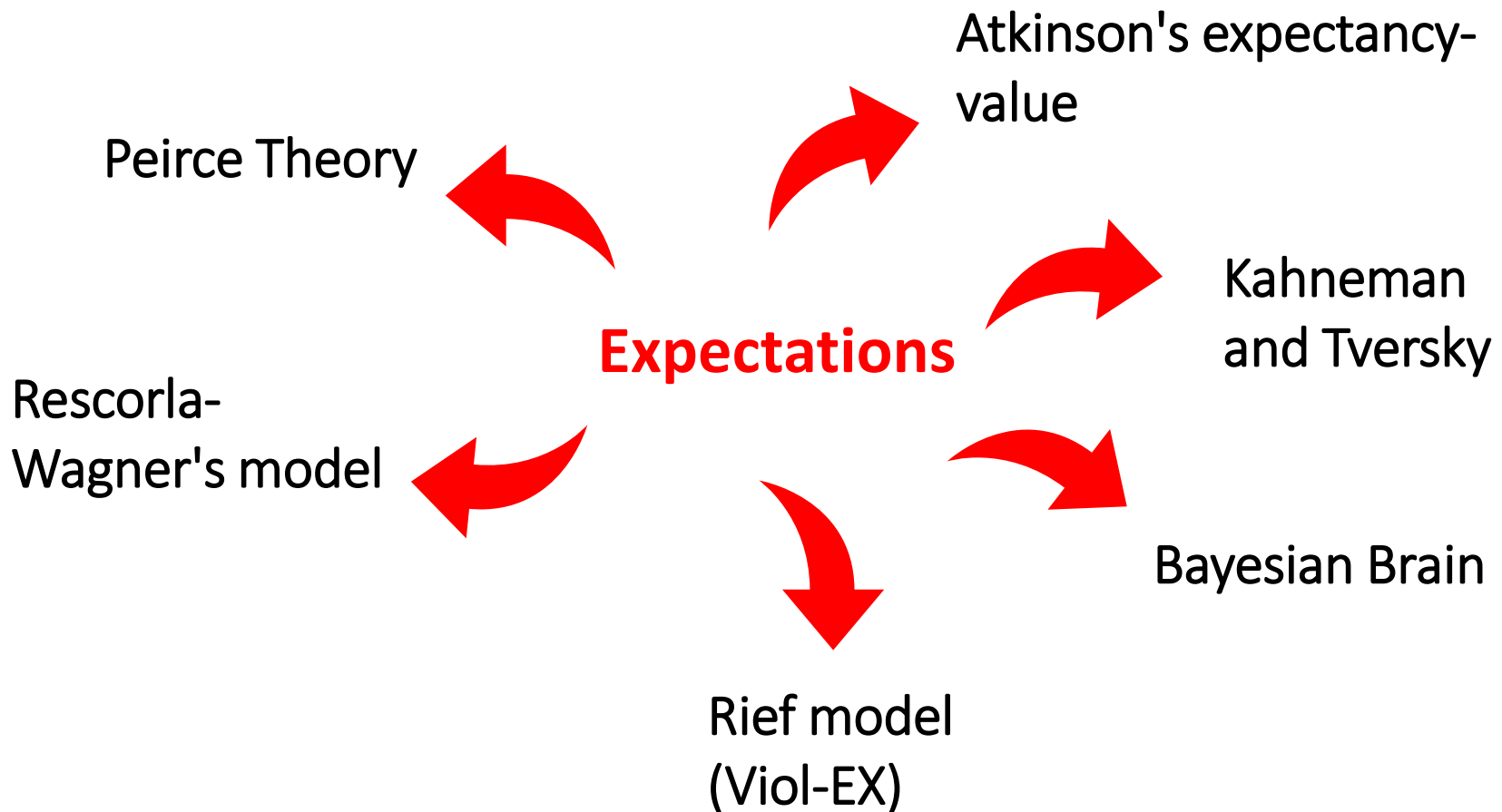
Expectation: Peirce's theory

- According to Peirce's theory (1839-1914), when one is in front of a sign (index, symbol or icon) we speak of "translation" to identify the process by which it is possible to **derive meaning from the particular sign**. Triadic relation of signs, object and interpretant

SYMBOL

INDEX

ICON

SIGNS

OBJECT that has to be interpreted

INTERPRETANT (idea or thought that interprets)

Colloca & Miller, 2003
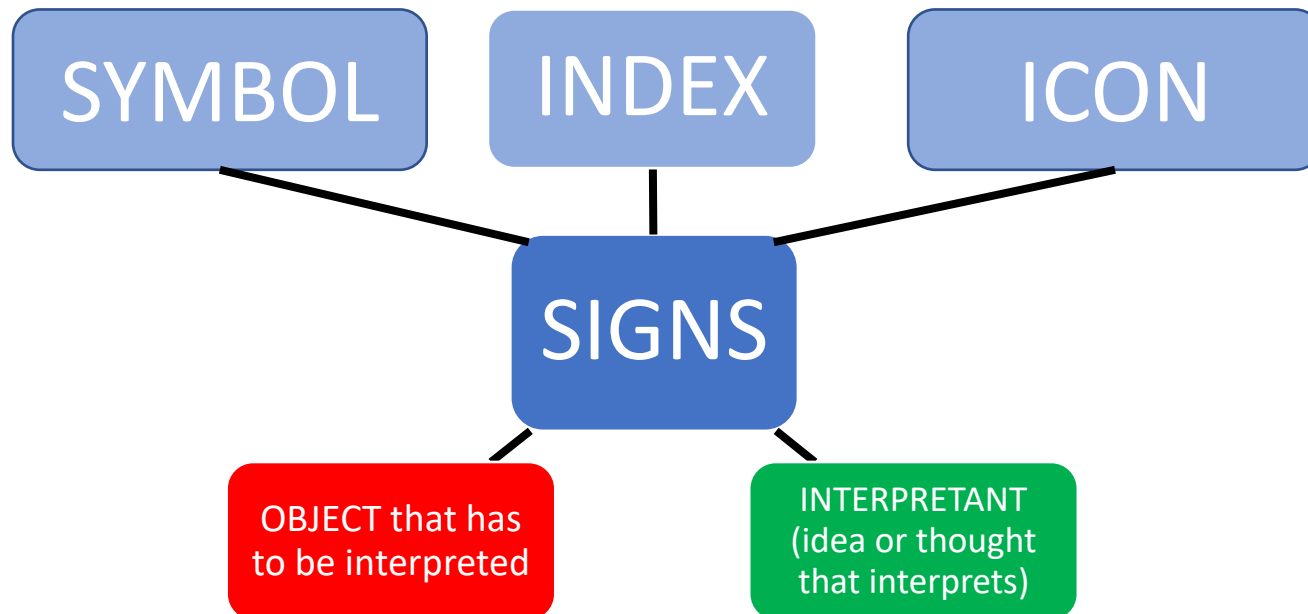
Expectation: Peirce's theory

Signs are anything **that elicits an interpretation of an object**. They are classified into 3 categories:

1. **Indexes** → signs that are dynamically connected with objects and with the senses and memories of the individuals to whom they serve as signs. They refer to a given object for the simple fact that there is a **relationship of concrete proximity between the index and the indicated object** (e.g. smoke indicates the presence of fire)

2. **Symbols** → signs that refer to the object according to **conventions** (so they are **arbitrary**!)

3. **Icons** →signs that refer to the object on the basis of a **similarity** between the sign and the object

= warning
→ arbitrary

= risk of fire →
similarity between the
sign and the object

Colloca & Miller, 2003

Expectation: Peirce's theory

- We actively interpret the signs of the objects that surround us

- This interpretation produces changes in our body that add to the changes produced by the object itself

Expectation: Atkinson's expectancy-value theory

- **Behaviors in stressful situations** can be predicted based on the interaction between the **expectation** of being able to cope with such situations, borrowed from past experiences, and the **subjective value** of the specific situation (Atkinson and Reitman, 1956)

> Behaviors in stressful situations:
>
> Expectation (past experiences)+ Subjective value

- In a care setting, <u>subjective value</u> is typically associated with the <u>hope of surviving the disease</u>, as well as with the <u>hope of reducing</u> pain and more generally symptoms associated with the disease.

- A better clinical outcome can be predicted if the **expected improvement** following treatment administration has a **high personal value** and if the patient has a **high sense of self-efficacy.**

Atkinson and Reitman, 1956; Horne and Weinman, 2002

Expectation: Kahneman and Tversky's prospect theory

- The idea behind these theories is the **balance between loss and gain**

- In decision-making, **potential losses tend to carry greater weight** than anticipated gains

- In a clinical setting, patient anxiety and concerns about treatments may be more relevant in predicting patient behavior than potential benefits of treatment

Kahneman and Tversky, 1979

Expectation: Rescorla-Wagner's model

- Expectations develop as a result of an **associative learning process.**

- According to the Rescorla-Wagner model, expectations are learned following trials (learning what to expect).

- The strength of expectations is given by the <u>number of trials that confirm the association</u>→**learning rate**

- **Learning** is reconceptualized in terms of **changes in expectations**

Rescorla, 1967

Expectation: ViolEx-model

- **Rief** et al., developed a model that conceptualizes how expectations influence different clinical outcomes and explains how the **violation of expectations** leads to behavior change or perseverance

- At the basis of the proposed model there is the interaction between EXPECTATIONS and CLINICAL CONTEXTS (e.g. going to the doctor for treatment).

- **Interaction** with the physician leads to **predictions**, **outcomes**, and **evaluations** of therapeutic outcome that can confirm or disconfirm pre-existing expectations.
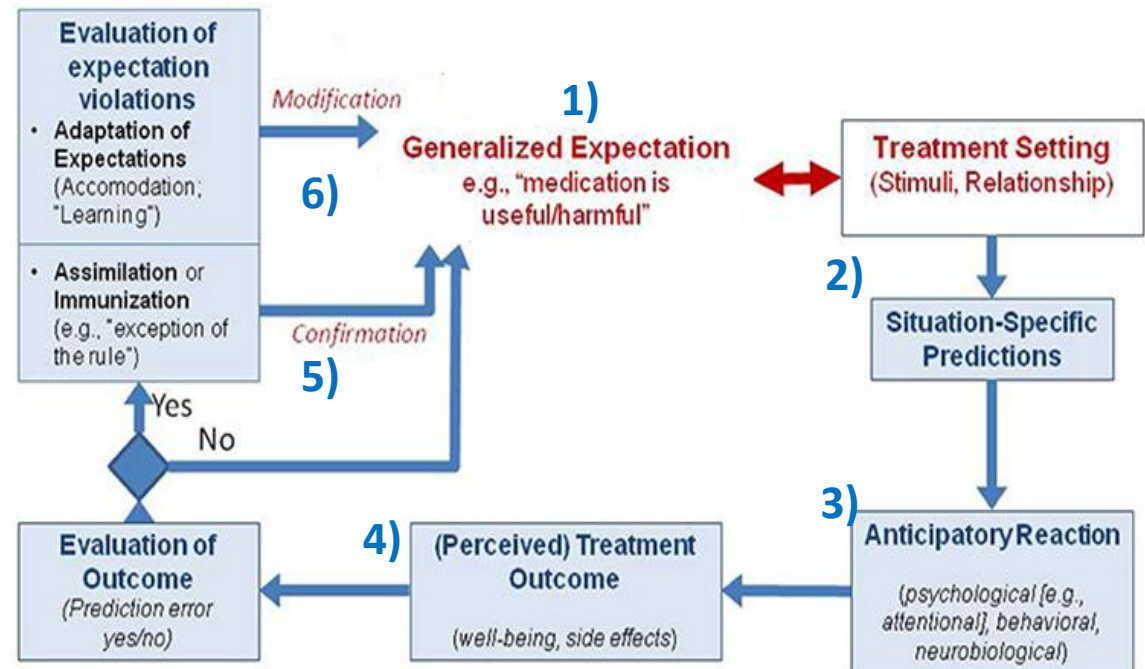
Rief et al., 2015

When we receive medical treatment:
1) Generalized pre-existing expectations→may amplify the effects of the treatment or worsen them (nocebo effects)
2) The interaction between **generalized** pre-existing expectations and the medical context leads to **specific predictions**,
3) Associated with typical **anticipatory anxiety reactions**
4) Once the treatment has been administered, **the patient evaluates the treatment to understand whether or not it corresponds to their expectations**
5) The more frequently positive expectations occur, the more stable generalized expectations will become **(confirmation)**
6) Conversely, if the expected outcome does not occur, expectations are **modified** as a result of expectation violation.. **The change can be more or less adaptive.**
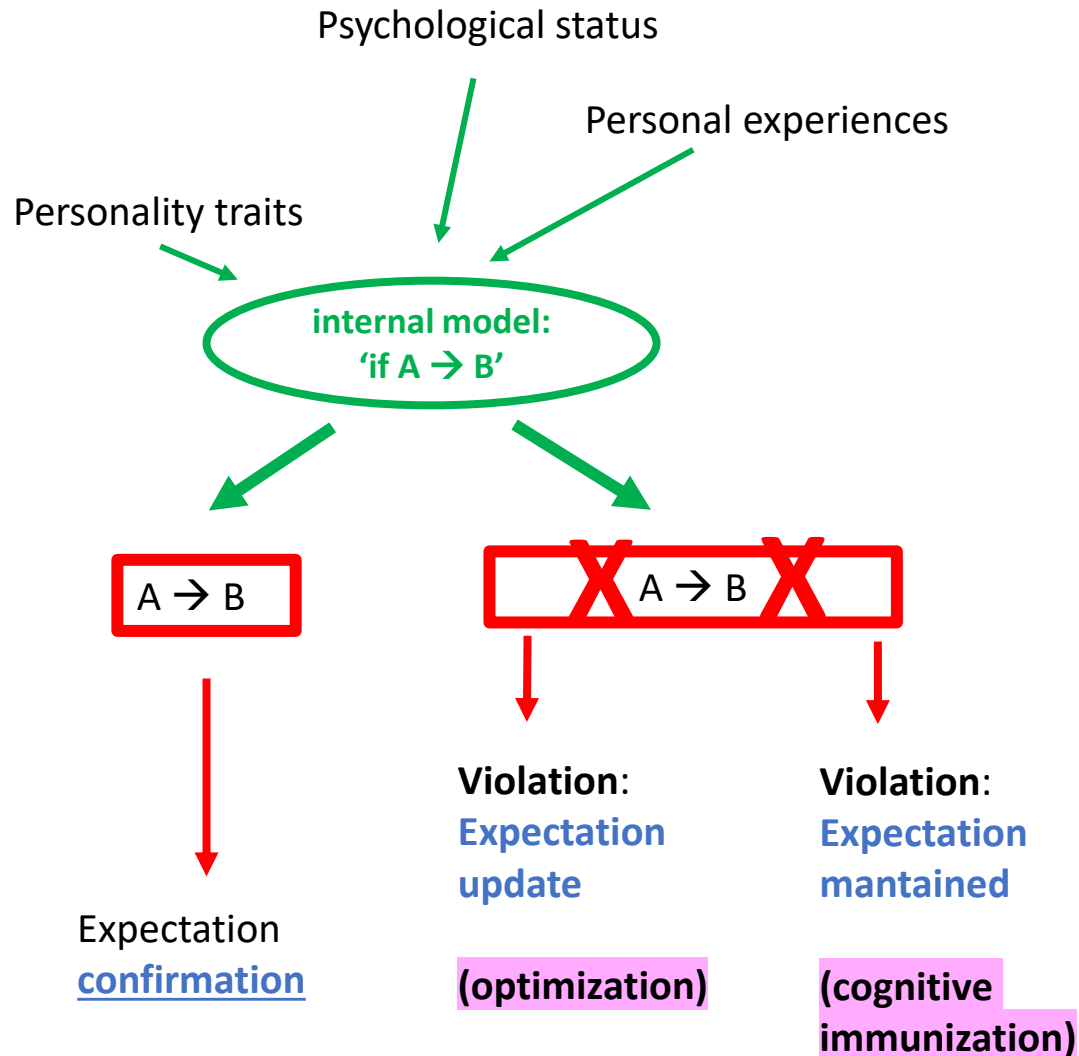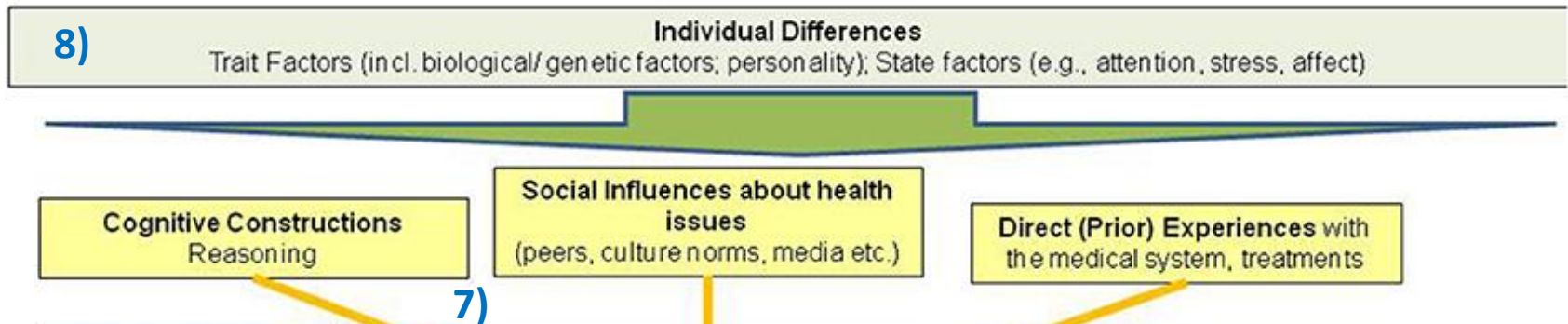
ViolEx-model

It is a crucial point for several aspects:
- Patients have expectations
- Doctors have expectations
- Doctors' and patients' expectations may differ
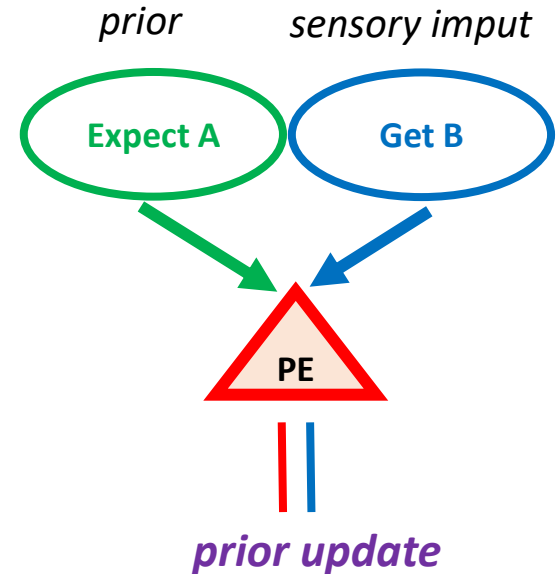- Patients saw other doctors and received other treatments

Rief and Petrie, 2016

ViolEX model

Psychological status

Personal experiences

Personality traits

internal model:
'if A → B'

A → B

X A → B X

Violation:
Expectation update

Violation:
Expectation mantained

Expectation
confirmation

(optimization)

(cognitive immunization)

?

Rossettini et al., 2022 (under review)

8) Individual Differences
Trait Factors (incl. biological/genetic factors; personality); State factors (e.g., attention, stress, affect)

Cognitive Constructions
Reasoning

7)

Social Influences about health issues
(peers, culture norms, media etc.)

Direct (Prior) Experiences with the medical system, treatments

7) The development of expectations is determined by at least three different factors:
   - **previous experience** (associative learning)
   - **social influences** (direct or indirect social learning via social media)
   - **cognitive processes specific to the individual patient**

8) Finally, generalized expectations are dependent on **genetic and psychological** traits and individual differences

Rief and Petrie, 2016
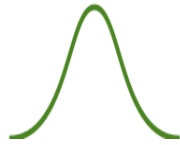
Bayesian Perspective

- Following the Bayesian perspective, our brain is a probabilistic machine that generates predictions (**priors**) about incoming **sensory stimuli**.

- When the **priors** update in relation to sensory experiences (**sensory input**), **posteriors** are generated, i.e. priors updated by the new evidence

- The discrepancy between Prior and Sensory Input is referred to as **Predictive ERROR**
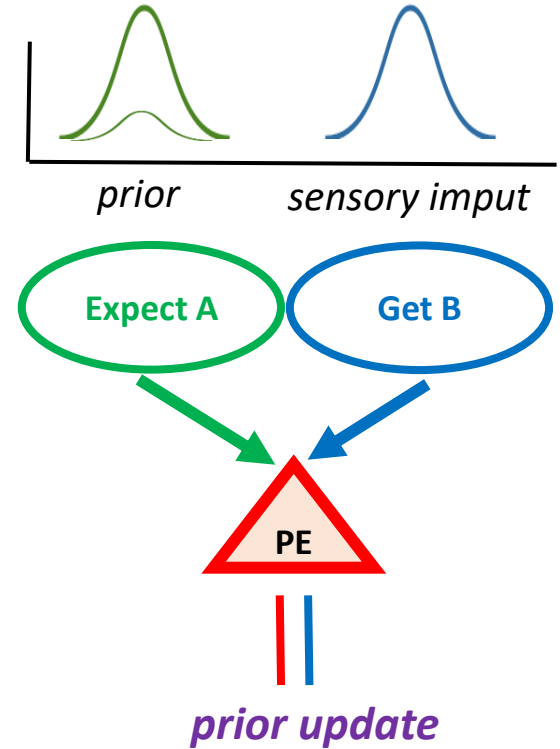
prior   *sensory imput*

Expect A   **Get B**

PE

prior update

(Brown et al., 2013;Buchel et al., 2014;Seth and Friston, 2016)

Bayesian Perspective

- Prior has different levels of accuracy

    - High accuracy → Reliable

    - Low accuracy → Unreliable

prior   sensory imput

Expect A   Get B

PE

prior update

(Brown et al., 2013;Buchel et al., 2014;Seth and Friston, 2016)

Bayesian Perspective

Rossettini et al., 2022 (under review)
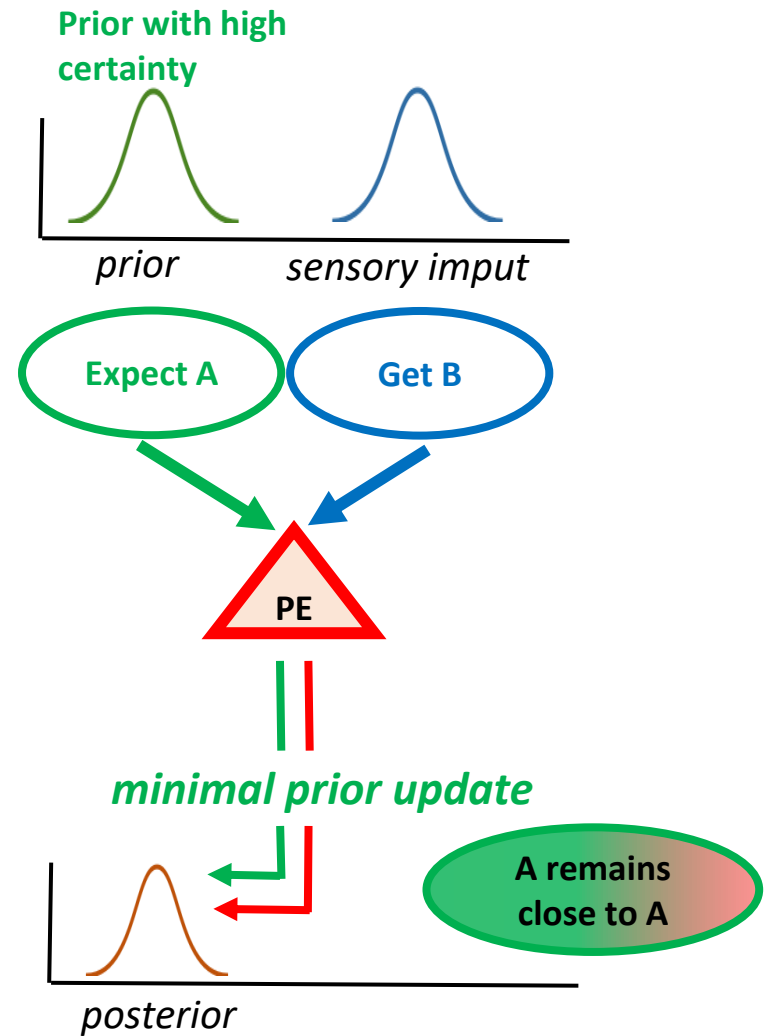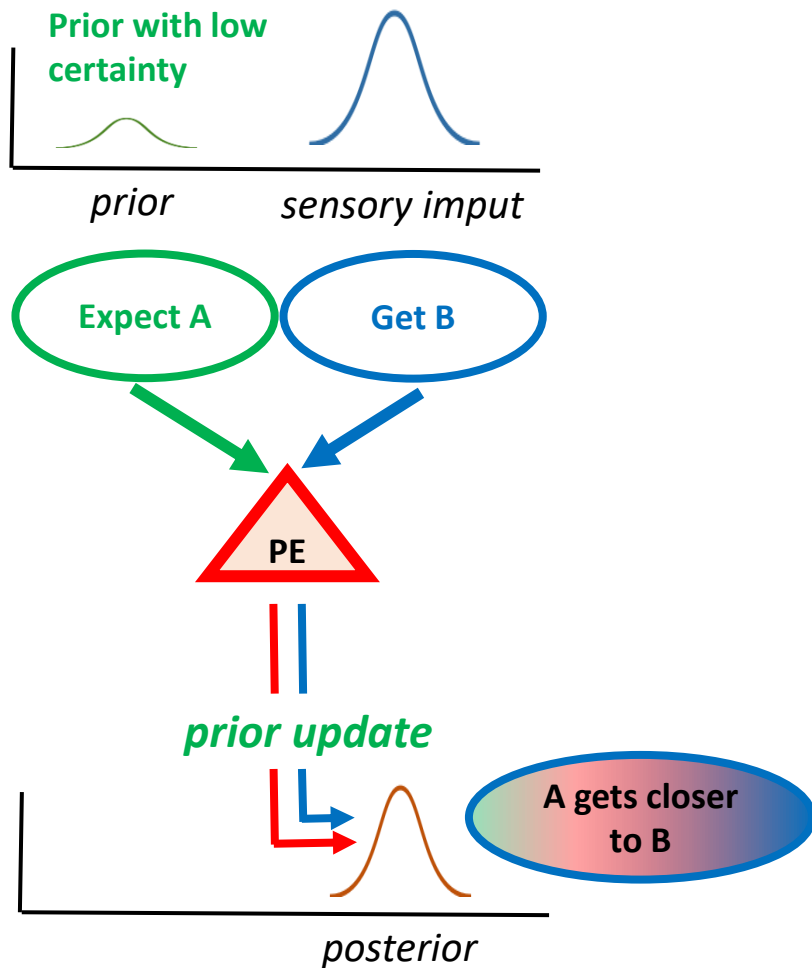
So why is it that, in certain cases, negative beliefs persist even after being disconfirmed?
According to Bayesian Perspective and ViolEx model

- Expectation violation followed by **update** → can be attributed to one's having a **prior with low precision** which is updated accordingly with the newly acquired evidence (i.e., according to this view, the patient who is shown that lifting their arm does not lead to their shoulder to break and therefore updates such dysfunctional belief, does not have a highly confident negative prior).

- Expectation violation followed by the maintenance of the **dysfunctional belief** → would be understood as the consequence of one's having a **highly precise prior** which is considered highly reliable and therefore, the newly acquired disconfirmatory evidence is not sufficient to disproof and update such strong prior. Indeed, the attribution of high certainty to such prior can motivate the engagement of higher-order cognitive strategies, such as cognitive immunization

Rossettini et al., 2022 (under review)

D) CLINICAL SCENARIO

PATIENT:
"I prefer not to lift my arm overhead because I have been told tendons can snap."

CLINICIAN:
"I see your concern, why don't we try some gentle movements together and see what happens?"

E) EXPECTATION UPDATE

Prior with low precision

PATIENT: "That was quite painful. Nothing has been torn or snapped. I think that if I keep on doing some exercises, it will eventually get better."

F) EXPECTATION MANTAINED

Prior with high precision

PATIENT: "The pain was not as bad as I expected and nothing has snapped but I think that was due to chance only. I am sure that if I do these movements repeatedly the tendons will snap one day or the other."

Rossettini et al., 2022 (under review)

PSYCHOLOGICAL MECHANISMS

- Theoretical aspects:
  - Expectation: models
  - **Conditioning**:
    - **Classical**
    - **Operant**
    - **Social**

- From theory to practice: placebo effect studies

Conditioning

- Behavioral psychology: different types of Learning

The 3 Major Types of Behavioral Learning

Classical Conditioning

A neutral stimulus is associated with a natural response

Operant Conditioning
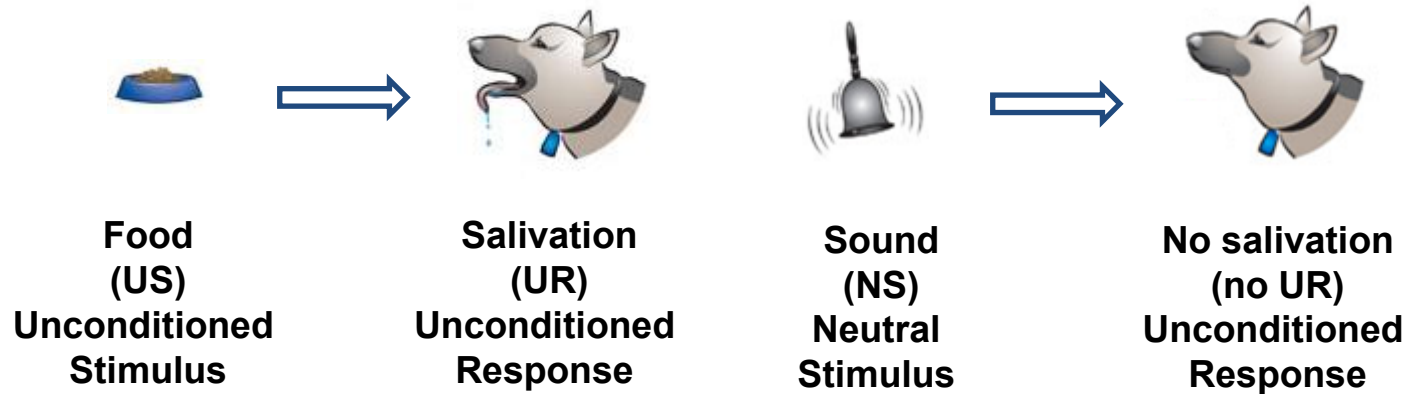
A response is increased or decreased due to reinforcement or punishment
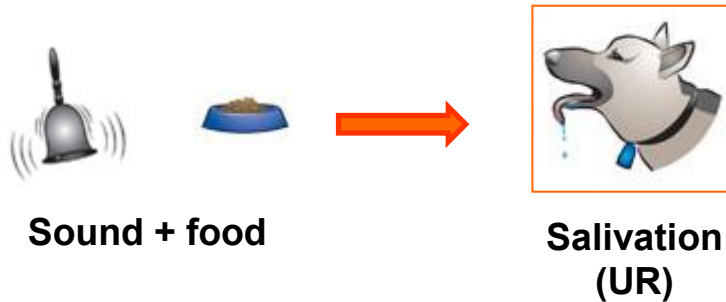
Observational Learning

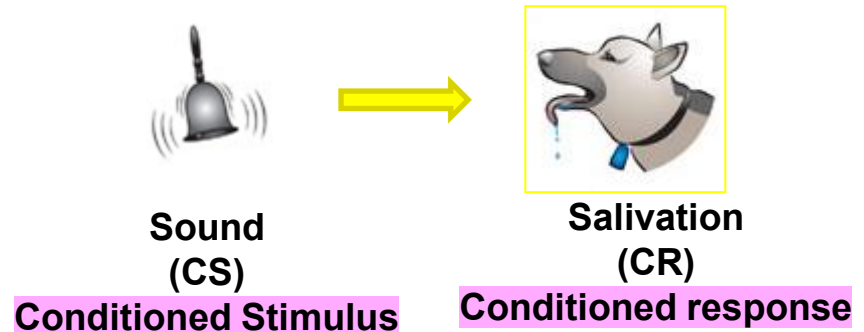Learning occurs through observation and imitation of others
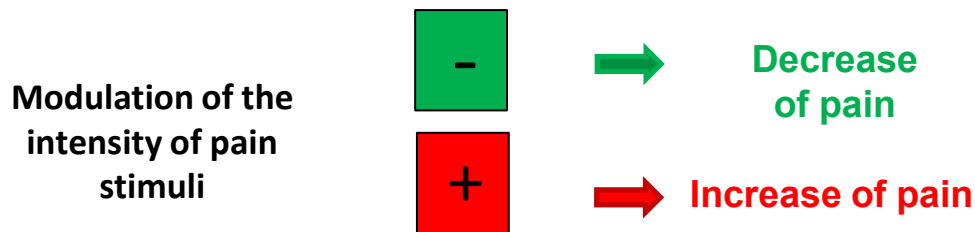
CLASSICAL CONDITIONING

BEFORE CONDITIONING

Food
(US)
Unconditioned
Stimulus

Salivation
(UR)
Unconditioned
Response

Sound
(NS)
Neutral
Stimulus

No salivation
(no UR)
Unconditioned
Response

ACQUISITION PHASE

Sound + food

Salivation
(UR)

RECALL PHASE

Sound
(CS)
Conditioned Stimulus

Salivation
(CR)
Conditioned response

Schedlowski et al. (2010) *Brain Behav Imm 24: 176-185*
Vits et al. (2011) *Phil. Trans. R. Soc. B 366: 1799-1807*

CLASSICAL CONDITIONING

ACQUISITION PHASE
co-occurrence of…

RE-RECALL PHASE

| MEDICATION / TREATMENT | + | CONTEXT | → | EFFECT |

THERAPEUTIC BENEFIT (pain reduction)

CONTEXT → EFFECT

THERAPEUTIC BENEFIT (pain reduction)

Chemotherapy + → **NAUSEA**

→ **NAUSEA**

Modulation of the intensity of pain stimuli

− → **Decrease of pain**

+ → **Increase of pain**

− → **Decrease of pain**

+ → **Increase of pain**

Schedlowski et al. (2010) *Brain Behav Imm* 24: 176-185
Vits et al. (2011) *Phil. Trans. R. Soc. B* 366: 1799-1807

Conditioning>> expectation
if we precondition a patient, the placebo effect is higher

SOCIAL CONDITIONING

- Learning mediated by the presence of a social context (observational)
    - Presence of an "actor" who simulates improvements or worsening
    - In the clinical context→ waiting room

Colloca et al., Philos Trans R Soc Lond B Biol Sci, 2011

Thoracotomized patients were treated with **buprenorphine on request** for 3 consecutive days, together with a basal intravenous infusion of saline solution.
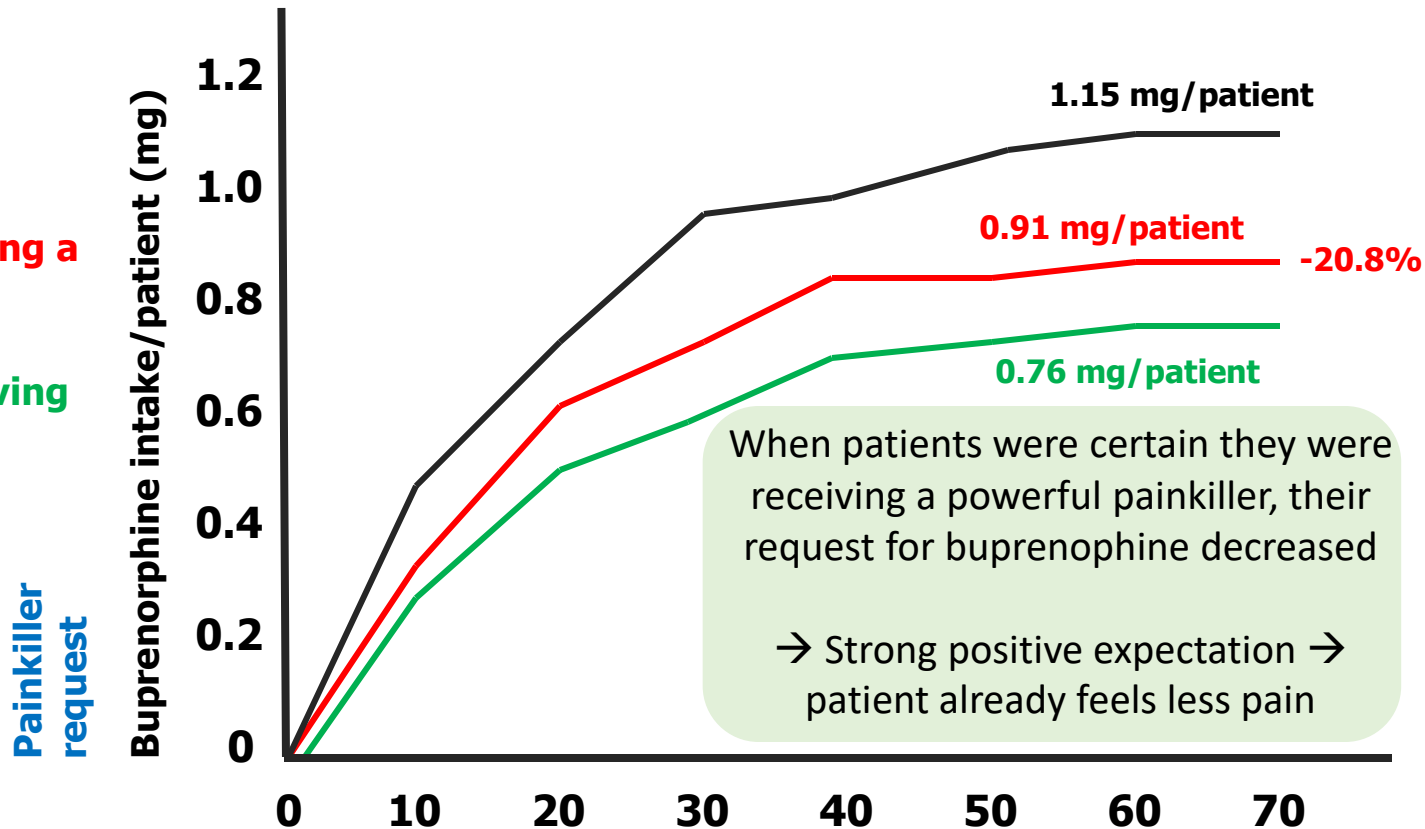
Post-surgery patients

The **symbolic meaning** of this basal infusion was changed in three different groups of patients.

NATURAL HISTORY

50% chance of receiving a painkiller

100% chance of receiving a painkiller

Painkiller request

Buprenorphine intake/patient (mg)

1.2
1.0
0.8
0.6
0.4
0.2
0

1.15 mg/patient

0.91 mg/patient

-20.8%

0.76 mg/patient

0   10   20   30   40   50   60   70

When patients were certain they were receiving a powerful painkiller, their request for buprenophine decreased

→ Strong positive expectation → patient already feels less pain

Pollo et al., 2001, Pain

Role of time expectation

Temporal expectations play a crucial role in modulating **when** and **how** pain is perceived
(study with a inert cream)
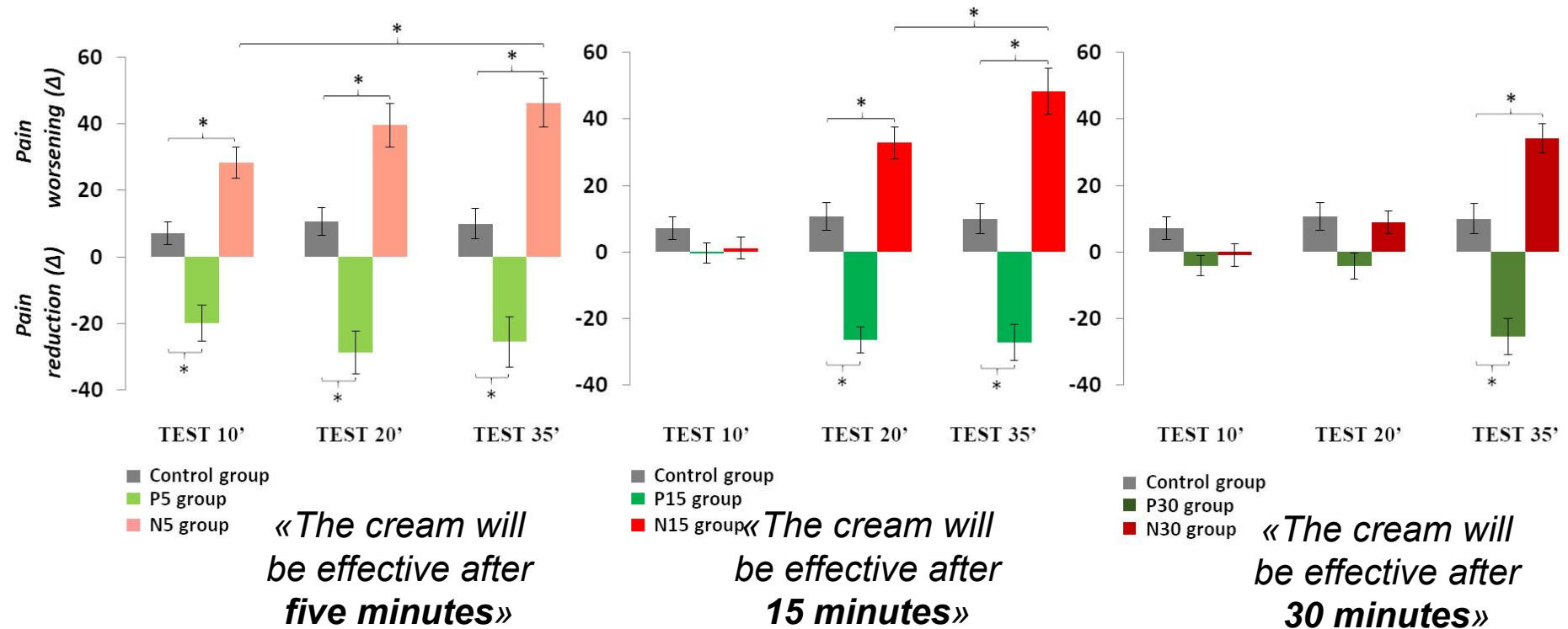
- Placebo effects emerge at the expected time and **remain stable**
- Nocebo effects emerge at the expected time and **increase over time**

Camerone et al., Psychosom Med, 2021

Social Learning vs Classical Conditioning vs Expectation

Learning from a model:
it can be observed that
another subject experiences
a reduction in pain following the activation of two
electrodes (sham placebo)

**NO DIFFERENCE BETWEEN SOCIAL LEARNING
AND CLASSICAL CONDITIONING**
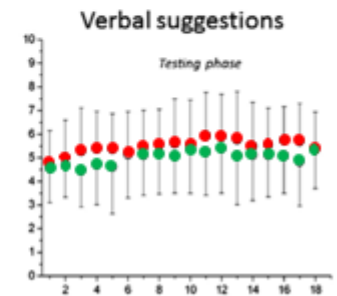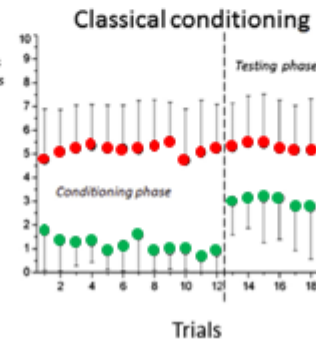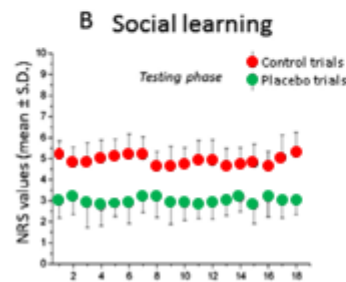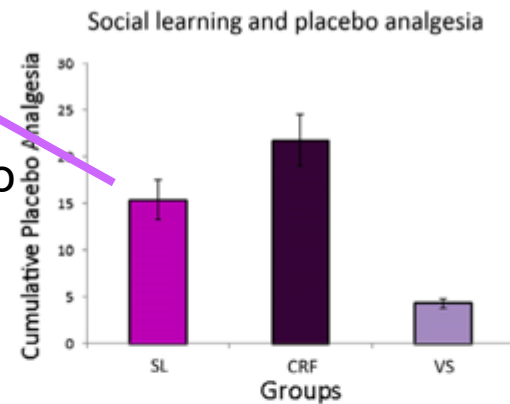
- **Direct experience and observation** are **more effective** than verbal suggestion alone
- Placebo effects can be **socially modulated**, not just individually

Colloca L, Benedetti F (2009) Pain 144:28–34.

Partial vs continuous reinforcements

Partial reinforcement and placebo analgesia

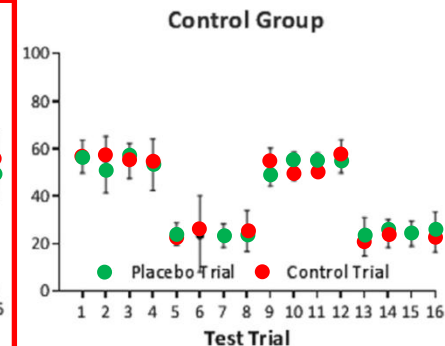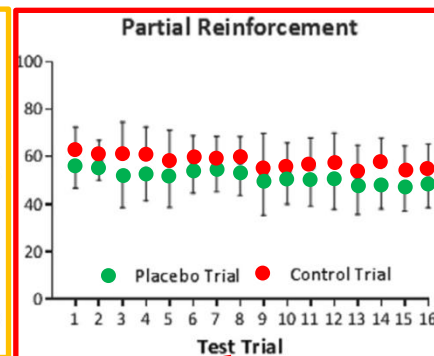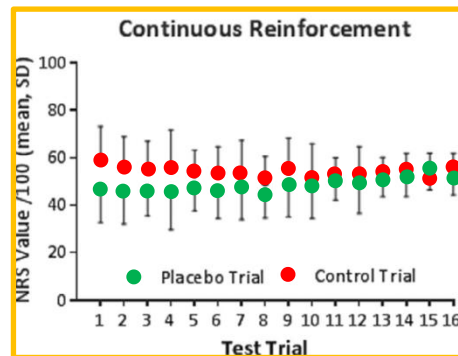**The placebo effect does not extinguish after partial reinforcement**

During the Acquisition phase, the placebo is always paired with the Pain reduction

B

During the Acquisition phase, the placebo is paired with the Pain reduction in 62% of trials
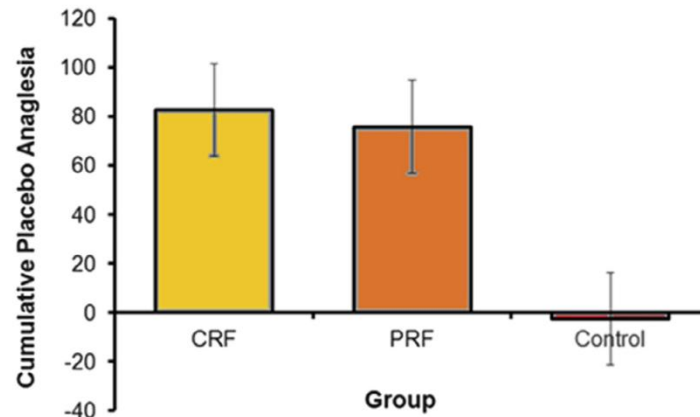
- Partial reinforcement (RPF) induces placebo analgesia that is more resistant to extinction than contiuous reinforcement (CRF)
- CRF produces stronger initial analgesia, but RPF leads to longer-lasting effects.

Au Yeung et al. (2014) Pain 155:1110–1117.